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DESIGN, SYNTHESIS AND CHEMICAL HYDROLYSIS STUDY OF CODRUGS OF PROPRANOLOL WITH METFORMIN.

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ABSTRACT

In the present study we have synthesized ester prodrugs (**Pa-h**) of Propranolol **(I)** by using pthalic anhydride and derivatives of succinic and maleic anhydride. Different codrugs **(COa-h)** were synthesized from prodrugs of propranolol. All the codrugs were characterized by melting point, FTIR, NMR and Mass Spectroscopy. The chemical hydrolysis of **COa-h** were investigated at the pH 1.2, 6.8 and 7.4. Presence of maleate, methyl maleate, dimethyl maleate and succinate group as linker possess high hydrolysis when compared to that of other substitutes. Among the synthesized codrugs, **COd** is found to be the best one among the series.

KEYWORDS: Chemical hydrolysis, codrugs, metformin, prodrugs, propranolol.

1. INDRODUCTION

Diabetes is a chronic disease, affecting nearly 6% of the world population. The incidence and prevalence of type 2 diabetes are increasing; it is projected that the total number of people with diabetes will rise to 366 million by 2030. The number of adults with hypertension is predicted to increase by 60% to a total of 1.56 billion people by 2025.[1]

Diabetes and high blood pressure are closely related diseases. They occur together so frequently that they are officially considered to be "comorbidities". Unfortunately, diabetes makes high blood pressure more difficult to treat, and high blood pressure makes diabetes even more dangerous.[2]

For patients suffering from one or more diseases, polypharmacy is very common for synergistic effects, to control the complications of the disease or adverse reactions of one of the drugs used. But polypharmacy may lead to more adverse or toxic reactions, potential duplication of therapy, increased cost and deceased quality of life etc.[3,4]

But instead of using multiple drugs separately in same or different forms, these drugs may be administered as single chemical entity as codrug or mutual prodrug.

Prodrugs, the pharmacologically inactive derivatives of active drugs, are designed to maximize the amount of active drug that reaches its site of action, through manipulation of the physicochemical, biopharmaceutical or pharmacokinetic properties of the drug.[5] Codrug or mutual prodrug is the type of carrier-linked prodrug, where the carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties and then subsequent enzymatic or nonenzymatic mechanism to release the active drug moiety. The term 'codrug' or 'Mutual Prodrug' refers to two or more therapeutic compounds bonded via a covalent chemical linkage. Regardless of being similar to prodrug it differs in having inactive group replacement by active group, which are coupled directly or indirectly (by a cleavable spacer).[6,7,8] The combination of two pharmacological moieties in a single molecule could be considered as a promising drug design strategy.[9] In general, a codrug can induce unique effects which a monomeric structure never shows.[10] The conjugation of two same pharmacophoric moieties could increase efficacy compared with that of the corresponding monomeric unit, while an conjugation of two dissimilar pharmacophores could elicit the corresponding effects derived from the individual units.[11] The second one will generate a synergic effect by modulating all together the two biological targets.[12,13] Codrug has improved absorption rate and can be easily transported to the target site of action. It has to be stable at the gastrointestinal level, but then it has to be hydrolyzed to provide two (or more) active drugs.[14] The mutual prodrugs are designed with improved physicochemical and pharmacological properties.[15]

Therefore in view of above findings, it is thought worthwhile to design and synthesize the codrugs of propranolol and metformin by altering their

physicochemical properties and thereby increasing the bioavailability.

2. MATERIALS AND METHODS

Propranolol was obtained as gift samples from Cadila Healthcare Limited, Ahmadabad (India). All solvents were of analytical grade and distilled before use. All the reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Melting points were determined by open capillary tubes and were uncorrected. FTIR spectra of the powdered compounds were recorded using ATR on a Bruker FTIR spectrophotometer and are reported in cm^{-1} and ^{1}H NMR spectra were recorded on a Bruker (300 MHz NMR) spectrophotometer using TMS as an internal reference (Chemical shift represented in δ ppm). Mass spectra were recorded on GC–MS QP5050A System (benchtop quadrupole mass spectrophotometer). Purity of the compound was checked on TLC plates using silica gel G as stationary phase and was visualized using iodine vapors or under UV chambers.

2.1. Synthetic studies

Synthesis of prodrugs of propranolol (Pa-h)

Propranolol **(I)** (1.69 mmoles) was stirred at 85-90°C with different anhydrides of dicarboxylic acid (5.00 mmoles) and dimethyl formamide (DMF) (1 ml) for a period of 12-15 h. The mixture was then cooled to room temperature, water (10 ml) was added and the solution was washed with ether to remove DMF and the amide derivatives. The aqueous solution was evaporated to yield **Pa-h**.[16] The schematic representation of synthesis of **Pa-h** by using various anhydrides dicarboxylic acid is shown in "**Figure 1**".

Synthesis of codrugs of propranolol prodrugs with metformin (COa-h)

A two-necked round bottom flask was equipped with a dean-stark apparatus topped with a reflux condenser and a nitrogen inlet. Propranolol prodrugs **(**6 mmoles), boric acid (1 g) and methanol (20 ml) were kept in the reaction vessel. To this stirred colorless mixture metformin (8.2 mmoles) was added in portions. The reaction mixture was heated at reflux for 16-18 h and water was collected in the dean-stark trap. The mixture was then poured into dichloromethane (10 ml) which led to the formation of precipitate. The obtained product was then dried in vacuum.[17] The schematic representation of synthesis of **COa-h** is shown in **Figure 1**.

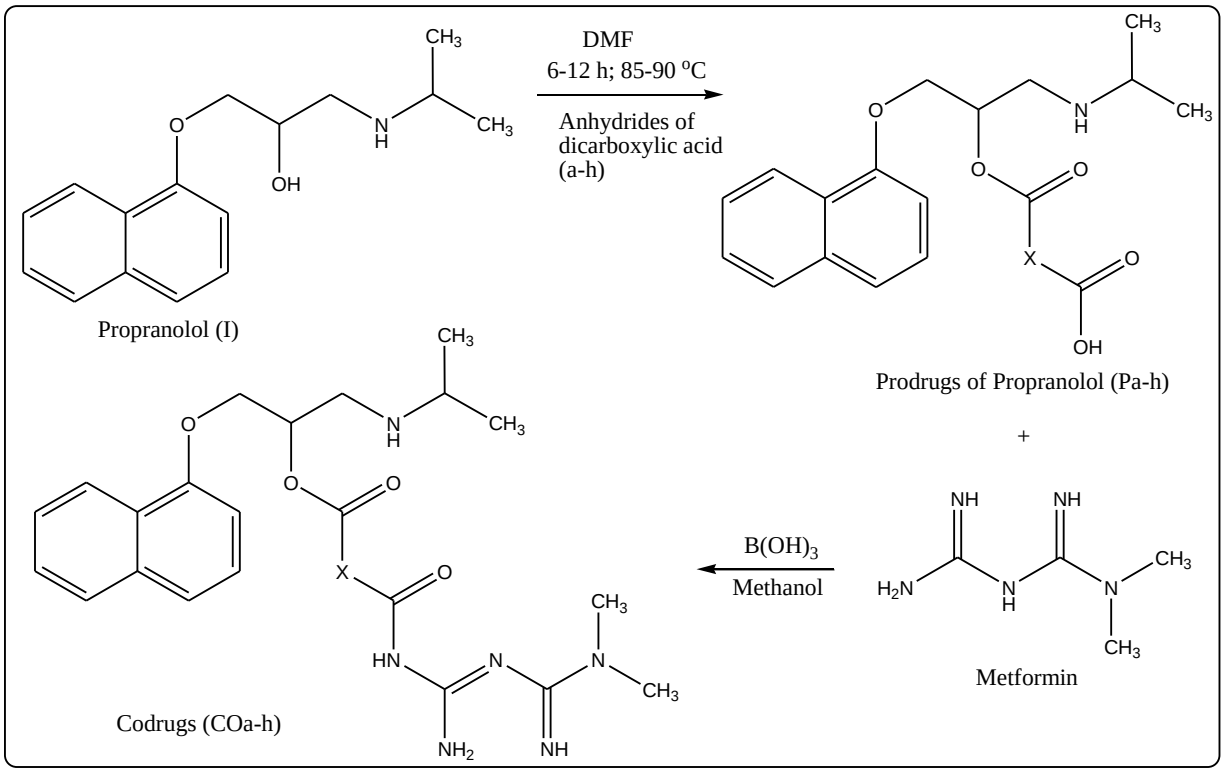
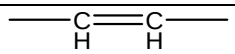
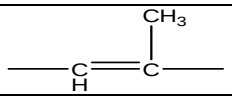
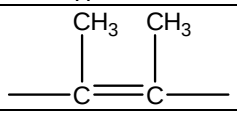
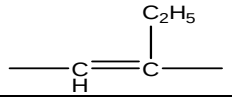
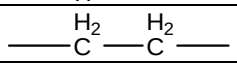
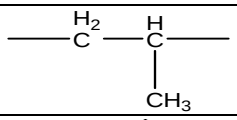
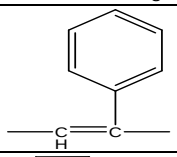
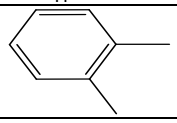
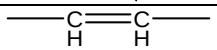
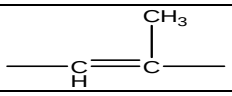
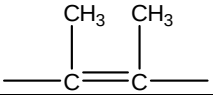
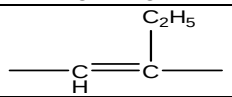
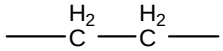
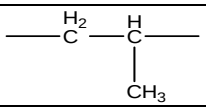
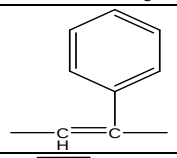
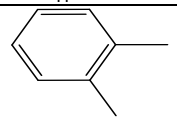


Figure 1: Schematic representation of synthesis of propranolol prodrugs (Pa-h) and codrugs (COa-h).

Sr. No.	Comp. Code	X
1	Pa	
2	Pb	
3	Pc	
4	Pd	
5	Pe	
6	Pf	
7	Pg	
8	Ph	
9	Co-a	
10	Co-b	
11	Co-c	
12	Co-d	
13	Co-e	
14	Co-f	
15	Co-g	
16	Co-h	

Physicochemical and spectral characterization of (Pa-h) and (COa-h)

But-2-enedioic acid mono-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Pa)

Yield: 90.74%; mp 194°C. FTIR (KBr) cm^{-1}: 3370.22 (N-H stre.), 3015.31 (Ar. C-H stre.), 2943.45 (Ali. C-H stre.), 2974.37 (O-H stre.), 1736.11 (C=O stre), 1550.29 and 1432.30 (Ar. C=C stre.), 1121.09 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 11.955 (s, COOH), 7.147-8.159 (m, 7H, Ar-H), 6.434-6.630 (d, C(O)CH), 6.162-6.349 (d, C(O)CH), 4.164-4.203 (m, 1H, OCH), 3.425-3.441 (d, 2H, OCH_2), 3.351 (s, 1H, NH), 2.978-3.125 (t, 2H, NCH_2), 2.538-2.547 (m, 1H, NCH),1.213-1.349 (d, 6H, $(CH_3)_2$). m/z 342 (M^+).

2-Methyl-but-2-enedioic acid 4-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Pb)
Yield: 91.72%; mp 178°C. FTIR (KBr) cm^{-1}: 3321.80 (N-H stre.), 3105.74 (Ar. C-H stre.), 2915.48 (Ali C-H stre.), 2820.35 (O-H stre.), 1777.22 (C=O stre), 1562.31 and 1404.28 (Ar. C=C stre), 1043.25 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 13.258 (s, 1H, COOH), 7.184-8.144 (m, 7H, Ar-H), 6.629 (s, C(O)CH), 4.178-4.203 (m, 1H, OCH), 3.672-3.694 (d, 2H, OCH_2), 3.434 (s, 1H, NH), 2.979-3.153 (t, 2H, NCH_2), 2.532-2.550 (m, 1H, NCH), 1.545 (s, 3H, $=C(CH_3)$,1.164-1.191 (d, 6H, $(CH_3)_2$). m/z 373 (M^+).

2,3-Dimethyl-but-2-enedioic acid mono-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Pc)
Yield: 88.11%; mp 242°C. FTIR (KBr) cm^{-1}: 3380.29 (N-H stre.), 3120.49 (Ar. C-H stre.), 2920.11 (Ali. C-H stre.), 2830.20 (O-H stre.), 1769.11 (C=O stre.), 1574.06 and 1480.27 (Ar. C=C stre.), 1150.26 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 11.614 (s, COOH), 7.162-8.125 (m, 7H, Arl-H), 4.153-4.203 (m, 1H, OCH), 3.715-3.725 (d, 2H, OCH_2), 3.535 (s, 1H, NH), 2.978-3.125 (t, 2H, NCH_2), 2.538-547 (m, 1H, NCH), 1.978 (s, 6H, $=C(CH_3)_2$), 1.268-1.299 (d, 6H, $(CH_3)_2$). m/z 387 (M^+).

2-Ethyl-but-2-enedioic acid 4-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Pd)
Yield: 87.24%; mp 219°C. FTIR (KBr) cm^{-1}: 3362.18 (N-H stre.), 3062.36 (Ar. C-H stre.), 2900.31 (Ali C-H stre.), 3150.49 (O-H stre.), 1720.48 (C=O stre), 1584.73 and 1451.88 (Ar. C=C stre.), 1083.24 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 11.578 (s, COOH), 6.614-8.184 (m, 7H, Ar-H), 6.435 (s, C(O)CH), 3.800-3.832 (m, 1H, OCH), 3.409 (s, 1H, NH), 3.211-3.409 (d, 2H, OCH_2), 2.971-3.039 (t, 2H, NCH_2), 2.527-2.567 (m, 1H, NCH)1.039-1.105 (d, 6H, $(CH_3)_2$), 1.534-1.715 (m, 2H, $\mathbf{CH_2}CH_3$), 1.441-1.529 (t, 3H, $CH_2\mathbf{CH_3}$)). m/z 387 (M^+).

Succinic acid mono-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Pe)
Yield: 83.78%; 202°C. FTIR (KBr) cm^{-1}: 3325.11 (N-H stre.), 3084.27 (Ar. C-H stre), 2960.36 (Ali. C-H stre.), 3147.84 (O-H stre.), 1710.15 (C=O stre.), 1610.19 and 1475.27 (Ar. C=C stre.), 1140.73 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 13.755 (s, COOH), 6.924-8.269 (m, 7H, Ar-H), 4.153-4.203 (m, 1H, OCH), 3.441 (s, 1H, NH), 3.268-3.299 (d, 2H, OCH_2), 3.113-3.167 (t, 2H, NCH_2), 2.607 ($NC(O)CH_2$), 2.527-2.553 (m, 1H, NCH), 1.826-1.845 (t, 2H, $OC(O)CH_2$), 1.745-1.759 (t, 2H, $OC(O)CH_2$), 1.110-1.138 (d, 6H, $(CH_3)_2$). m/z 346 (M^+).

2-Methyl-succinic acid 4-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Pf)
Yield: 87.74%; mp 210°C. FTIR (KBr) cm^{-1}: 3375.27 (N-H stre.), 3110.36 (Ar. C-H stre.), 2921.55 (Ali. C-H stre.), 3215.49 (O-H stre.), 1739.59 (C=O stre.), 1605.13 and 1463.27 (Ar. C=C stre.), 1092.24 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 11.733 (s, COOH), 7.337-8.222 (m, 7H, Ar-H), 4.192-4.249 (m, 1H, OCH), 4.130-4.143 (d, 2H, OCH_2), 3.308 (s, 1H, NH), 3.000-3.009 (m, 1H, NC(O)CH), 2.970-2.979 (t, 2H, NCH_2), 2.873-2.936 (m, 1H, NCH), 2.794-2.803 (d, 2H $OC(O)CH_2$), 1.536-1.544 (d, 3H, $C\text{-}CH_3$), 1.110-1.138 (d, 6H, $(CH_3)_2$). m/z 372 (M^+).

2-Phenyl-succinic acid 4-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Pg)
Yield: 84.33%; mp 191°C. FTIR (KBr) cm^{-1}: 3325.26 (N-H stre.), 3084.68 (Ar. C-H stre.), 2960.06 (Ali. C-H stre.), 3147.03 (O-H stre.), 1710.27 (C=O stre.), 1610.11 and 1475.29 (Ar. C=C stre.), 1140.11 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 11.985 (s, COOH), 8.023 (s, 1H, NH), 7.535-8.184 (m, 12H, Ar-H), 6.614-7.177 m, 3H, Ar-H), 6.435 (s, C(O)CH), 4.153-4.203 (m, 1H, OCH), 3.409 (s, 1H, NH), 3.141-3.211 (d, 2H, OCH_2), 2.971-3.105 (q, 2H, NCH_2), 2.527-2.567 (m, 1H, NCH), 1.102-1.212 (d, 6H, $(CH_3)_2$). m/z 434 (M^+).

Phthalic acid mono-[1-(isopropylamino-methyl)-2-(naphthalen-1-yloxy)-ethyl] ester (Ph)
Yield: 76.19%, mp 233°C. FTIR (KBr) cm^{-1}: 3352.23 (N-H stre.), 3081.41 (Ar C-H stre.), 2920.86 (Ali C-H), 2838.74 (O-H stre.), 1762.59 (C=O stre.), 1582.52 and 1474.35 (Ar C=C stre.), 1453.26, 1383.27 (NO_2), 1163.35 (C-O-C stre.). ^{1}H NMR (DMSO, δ ppm) 13.849 (s, COOH), 8.166-8.269 (m, 4H, Ar-H), 7.384-7.849 (m, 7H, Ar-H), 3.832 (s, 1H, NH), 3.377-3.441 (m, 1H, OCH), 3.268-3.299 (d, 2H, OCH_2), 3.113-3.167 (t, 2H, NCH_2), 2.523-2.553 (m, 1H, NCH), 1.300-1.326 (d, 6H, $(CH_3)_2$). m/z 407 (M^+).

1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-yl4-(3-(N,N-dimethylcarbamimidoyl)guanidino)-4-oxobut-2-enoate (COa)
Yield: 66.19%, mp 259°C. FTIR (KBr) cm^{-1}: 3370.06 (N-H stre), 3022.27 (Ar C-H stre.), 2941.36 (Ali. C-H stre.), 1687.69 (C=O stre.), 1643.58 (C=N stre.), 1575.49 & 1451.67 (Ar C=C stre.), 1204.06 (C-O-C stre.), 1110.14 (C-N). ^{1}H NMR (DMSO, δ ppm) 8.184 (s, 1H, C(O)NH), 7.754-7.868 (m, 3H, Ar-H), 7.434 (s, 2H, NH_2), 6.682-7.273 (m, 4H, Ar-H), 6.409 (s, 1H, C=NH), 6.377-6.393 (d, C(O)CH), 6.162-6.216 (d, C(O)CH), 4.153-4.203 (m, 1H, OCH), 3.441-3.525 (d, 2H, OCH_2), 3.351 (s, 1H, NH), 2.745-2.759 (t, 2H, NCH_2), 2.525-2.551 (m, 1H, NCH), 2.337 (s, 6H, $N(CH_3)_2$), 1.273-1.349 (d, 6H, $(CH_3)_2$). m/z 455 (M^+).

(1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-yl 4-(3-(N,N-dimethylcarbamimidoyl)guanidino)-3-methyl-4-oxobut-2-enoate (COb)
Yield: 75.96%; mp 229°C. FTIR (KBr) cm^{-1}: 3366.10 (N-H stre.), 3024.16 (Ar. C-H stre.), 2936.38 (Ali. C-H stre.), 1678.21 (C=O stre.), 1630.22 (C=N Stre.), 1503.38 & 1443.49 (Aromatic C=C stre.), 1234.36 (C-O-C stre.), 1074.57 (C-N). ^{1}H NMR (DMSO, δ ppm) 8.144 (s, 1H, C(O)NH), 7.715-7.748 (m, 3H, Ar-H), 7.578 (s, 2H, NH_2), 6.629-7.384 (m, 4H, Ar-H), 6.393 (s, 1H, C=NH), 6.178 (s, C(O)CH), 4.164-4.203 (m, 1H, OCH), 3.745-3.759 (d, 2H, OCH_2), 3.389 (s, 1H, NH), 2.826-

2.845 (t, 2H, NCH_2), 2.536-2.5501 (m,1H, NCH), 2.425 (s, 6H, $N(CH_3)_2$, 1.542 (s, 3H, $C(CH_3)$,1.057-1.099 (d, 6H, $(CH_3)_2$). m/z 485 (M^+).

1-(isopropylamino)-3-(naphthalen-1-yloxy) propan-2-yl 2-((N-(N,N-dimethylcarbamimidoyl) carbamimidoyl)carbamoyl)benzoate (COc)

Yield: 75.96%; mp 229°C. FTIR (KBr) cm^{-1}: 3374.44 (N-H stre.), 3050.79 (Ar C-H stre.), 2903.22 (Ali C-H stre.), 1690.30 (C=O stre.), 1641.72 (C=N stre.), 1583.36 & 1458.68 (Ar C=C stre.), 1212.35 (C-O-C stre.), 1121.10 (C-N stre.). ^{1}H NMR (DMSO, δ ppm) 8.184 (s, 1H, C(O)NH), 7.735-7.848 (m, 3H, Ar-H), 7.662 (s, 2H, NH_2), 6.759-7.566 (m, 4H, Ar-H), 6.441 (s, 1H, C=NH), 4.203-4.351 (m, 1H, OCH), 3.745-3.753 (d, 2H, OCH_2), 3.435 (s, 1H, NH), 2.45-2.759 (t, 2H, NCH_2), 2.541-2.553 (m, 1H, NCH), 2.310 (s, 6H, $N(CH_3)_2$), 1.832 (s, 6H, $=C(CH_3)_2$), 1.337-1.351 (d, 6H, $(CH_3)_2$). m/z 499 (M^+).

1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-yl 4-(3-(N,N-dimethylcarbamimidoyl)guanidino)-2,3-dimethyl-4-oxobut-2-enoate (COd)

Yield: 72.87%; mp 229°C. FTIR (KBr) cm^{-1}: 3379.06 (N-H stre.), 3063.36 (Ar. C-H stre.), 2916.27 (Ali C-H stre.), 1708.49 (C=O stre.), 1652.37 (C=N stre.), 1593.29 & 1462.29 (Ar C=C stre.), 1221.27 (C-O-C stre.), 1174.38 (C-N stre.). ^{1}H NMR (DMSO, δ ppm) 8.216 (s, 2H, C(O)NH), 7.725-7.748 (m, 3H, Ar-H), 7.715 (s, 2H, NH_2), 6.614-7.543 (m, 4H, Ar-H), 6.435 (s, 1H, C=NH), 4.300-4.326 (m, 1H, OCH), 3.745-3.753 (d, 2H, OCH_2), 3.409 (s, 1H, NH), 2.826-2.845 (t, 2H, NCH_2), 2.745-2.767 (m, 1H, NCH), 2.435 (s, 6H, $N(CH_3)_2$), 1.743-1.767 (m, 2H, $=C(CH_2)$), 1.538-1.547 (t, 3H, $C(CH_3)$),1.090-1.125 (d, 6H, $(CH_3)_2$). m/z 499 (M^+).

1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-yl 4-(3-(N,N-dimethylcarbamimidoyl)guanidino)-2,3-dimethyl-4-oxobut-2-enoate (COe)

Yield: 68.35%; mp 189°C. FTIR (KBr) cm^{-1}: 3393.48 (N-H stre.), 3074.57 (Ar. C-H stre.), 2893.37 (Ali. C-H stre.), 1745.48 (C=O stre.), 1670.57 (C=N stre.), 1584.76 & 1482.78 (Ar C=C stre.), 1230.64 (C-O-C stre.), 1144.37 (C-N stre.). ^{1}H NMR (DMSO, δ ppm) 8.269 (s, 1H, C(O)NH), 7.715-7.748 (m, 3H, Ar-H), 7.496 (s, 2H, NH_2), 6.924-7.384 (m, 4H, Ar-H), 6.630 (s, 1H, C=NH), 4.203-4.351 (m, 1H, OCH), 4.153-4.164 (d, 2H, OCH_2), 3.441 (s, 1H, NH), 2.826-2.845 (t, 2H, NCH_2), 2.745-2.767 (m, 1H, NCH), 2.680-2.694 (t, 2H, $NC(O)CH_2$), 2.541-2.55 (t, 2H, $OC(O)CH_2$), 2.523-2.532 (t, 2H, $OC(O)CH_2$), 2.423 (s, 6H, $N(CH_3)_2$),1.300-1.316 (d, 6H, $(CH_3)_2$). m/z 457 (M^+).

1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-yl4-(3-(N,N-dimethylcarbamimidoyl) guanidino)-4-oxobutanoate (COf)

Yield: 73.54%; mp 221°C. FTIR (KBr) cm^{-1}: 3386.68 (N-H stre.), 3124.05 (Ar. C-H stre.), 2902.51 (Ali C-H stre.), 1764.35 (C=O stre.), 1679.38 (C=N stre.), 1600.49 & 1483.51 (Ar C=C stre.), 1211.44 (C-O-C stre.), 1109.59 (C-N stre.). ^{1}H NMR (DMSO, δ ppm) 8.288 (s, 1H, C(O)NH), 7.894-8.140 (m, 3H, Ar-H), 7.769 (s, 2H, NH_2), 6.894-7.466 (m, 4H, Ar-H), 6.435 (s, 1H, C=NH), 4.155-4.213 (m, 1H, OCH), 4.140-4.143 (d, 2H, OCH_2), 3.308 (s, 1H, NH), 3.000-3.296 (m, 1H, NC(O)CH), 2.889-2.920 (t, 2H, NCH_2), 2.773-2.824 (m, 1H, NCH), 2.441 (s, 6H, $N(CH_3)_2$), 2.337-2.376 (d, 2H $OC(O)CH_2$), 1.126-1.138 (d, 3H, $C-CH_3$), 1.110-1.122 (d, 6H, $C(CH_3)_2$). m/z 483 (M^+).

1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-yl 4-(3-(N,N-dimethylcarbamimidoyl) guanidino)-4-oxo-3-phenylbut-2-enoate (COg)

Yield: 83.10%; mp 194°C. FTIR (KBr) cm^{-1}: 3390.29 (N-H stre.), 3081.20 (Ar C-H stre.), 2922.22 (Ali. C-H stre.), 1734.47 (C=O stre.), 1675.59 (C=N stre), 1605.78 & 1475.96 (Ar C=C stre.), 1243.21 (C-O-C stre.), 1140.59 (C-N stre.). ^{1}H NMR (DMSO, δ ppm) 8.435 (s, 2H, C(O)NH), 7.715-7.985 (m, 5H, Ar-H), 7.604 (s, 2H, $-NH_2$), 6.754-7.201 (m, 7H, Ar-H), 6.614 (s, 1H, C=NH), 6.409 (s, 1H, CO-(CH)=C), 4.384 (m, 1H, OCH), 3.745-3.753 (d, 2H, OCH_2), 3.496 (s, 1H, NH), 2.845 (t, 2H, NCH_2), 2.541-2.559 (m, 1H, NCH), 2.468 (s, 6H, $N(CH_3)_2$), 1.105-1.141 (d, 6H, $C(CH_3)_2$), m/z 544 (M^+).

1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-yl-2-((N'-(N,N-dimethylcarb amimidoyl)carbamimidoyl)carbamoyl)benzoate (COh)

Yield: 68.46%; mp 175°C. FTIR (KBr) cm^{-1}: 3381.37 (N-H stre.), 3089.58 (Ar C-H stre.), 2900.41 (Ali C-H stre.), 1755.25 (C=O stre.), 1670.37 (C=N stre.), 1614.88 & 1480.47 (Ar C=C stre.), 1472.69 and 1381.77 (NO_2), 1210.80 (C-O-C stre.), 1129.55 (C-N). ^{1}H NMR (DMSO, δ ppm) 8.578 (s, 1H, C(O)NH), 7.745-8.167 (m, 7H, Ar-H), 7.680 (s, 2H, NH_2), 6.826-7.409 (m, 7H, Ar-H), 6.213 (s, 1H, C=NH), 4.377-4.409 (m, 1H, OCH), 3.753-3.759 (d, 2H, OCH_2), 3.559 (s, 1H, NH), 2.832-2.849 (t, 2H, NCH_2), 2.753-2.767 (m, 1H, NCH), 2.435 (s, 6H, $N(CH_3)_2$),1.054-1.141 (d, 6H, $C(CH_3)_2$). m/z 519 (M^+).

a. Chemical hydrolysis studies

Hydrolytic behavior of synthesized co-drugs was studied in Simulated Gastric Fluid (pH 1.2; USP 1970); Simulated Intestinal Fluid (pH 6.8); Simulated Plasma Fluid (pH 7.4; USP 1970).[18] The hydrolysis was performed by using USP-II paddle apparatus at a rotational speed of 50 rpm. 900 ml solution of pH 1.2, 6.8 and 7.4 were used as dissolution media and maintained at 37±1°C. 1 ml of the hydrolysis medium was taken out at zero minute and every 15 min. for 120 min. 1 ml of the pH solution was added to the dissolution vessel. The sample withdrawn was subjected for HPLC analysis using Phenomenex Luna C_{18} column (250 mm x 4.6 mm id, 5 µm particle size), LC solutions software and mobile phase acetonitrile: water 70:30. Flow rate of mobile phase was kept at 1 mL/min at pressure 120-135 psi and UV detector (SPD-20A with D_2 lamp) was used and retention time and peak area were noted at 232 nm.

The comparative study of rate of hydrolysis is shown as follows.

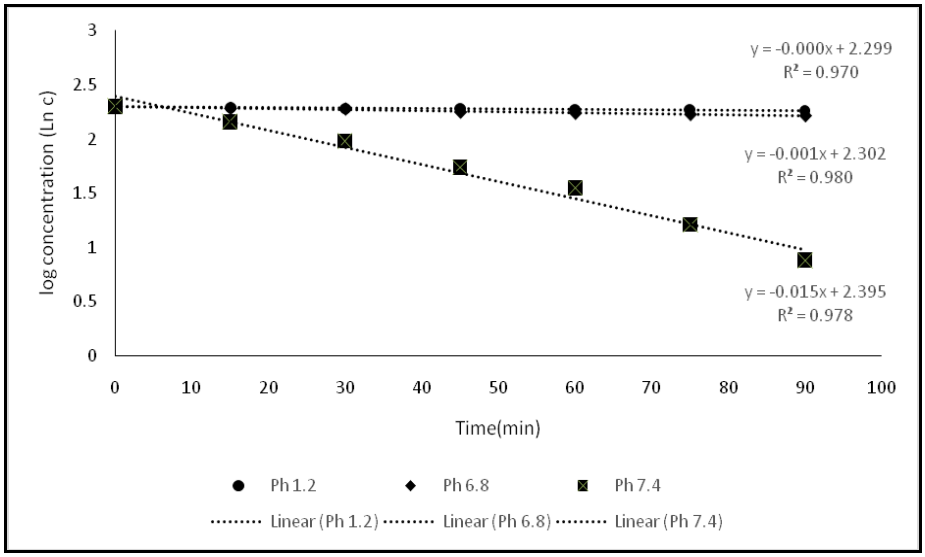


Figure 2: The hydrolysis rate of compound COa at different pH values.

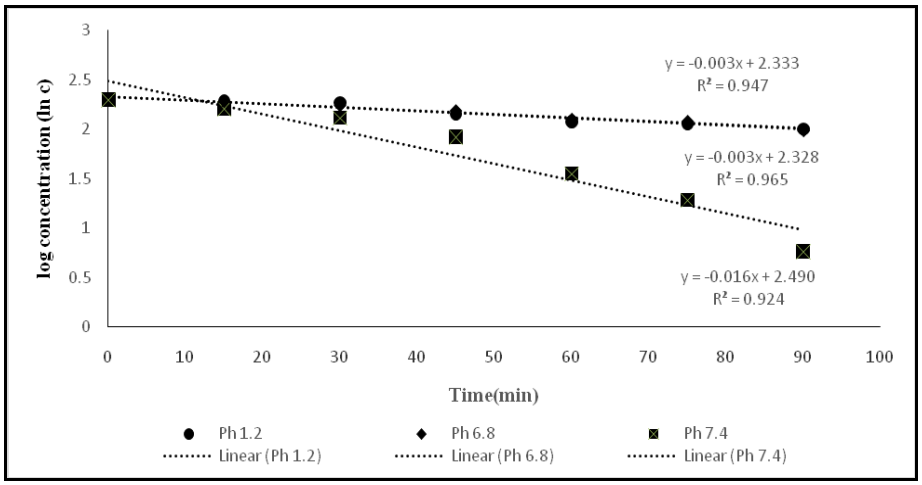


Figure 3: The hydrolysis rate of compound COb at different pH values.

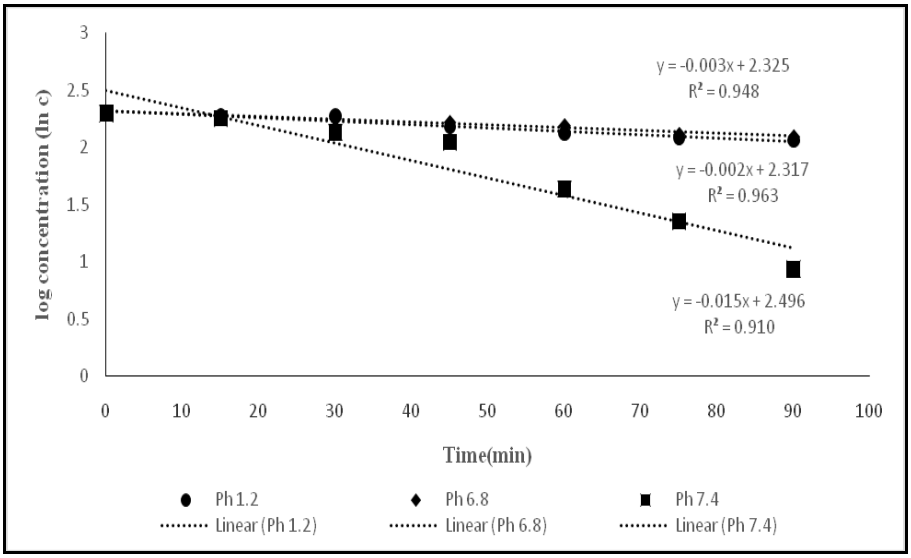


Figure 4: The hydrolysis rate of compound COc at different pH values.

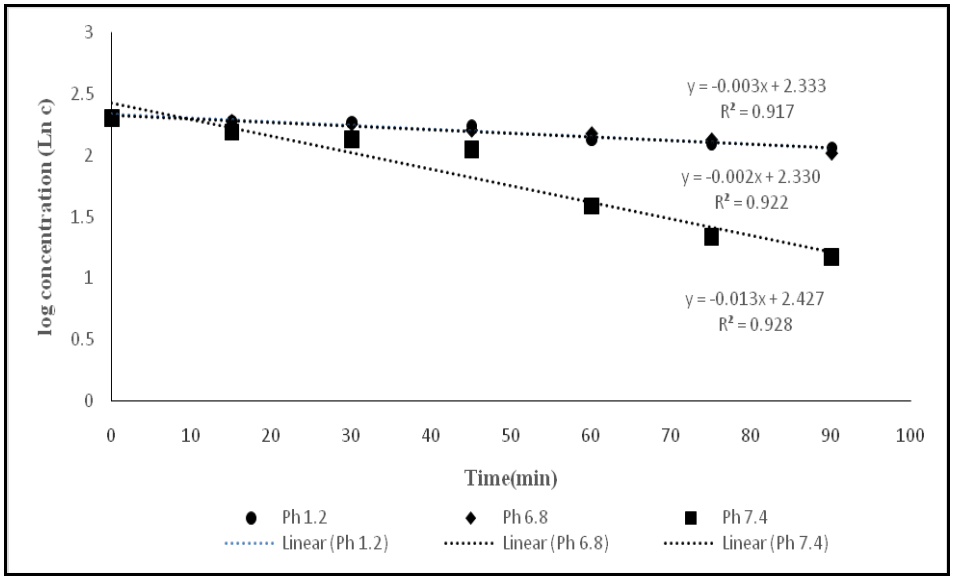


Figure 5: The hydrolysis rate of compound COd at different pH values.

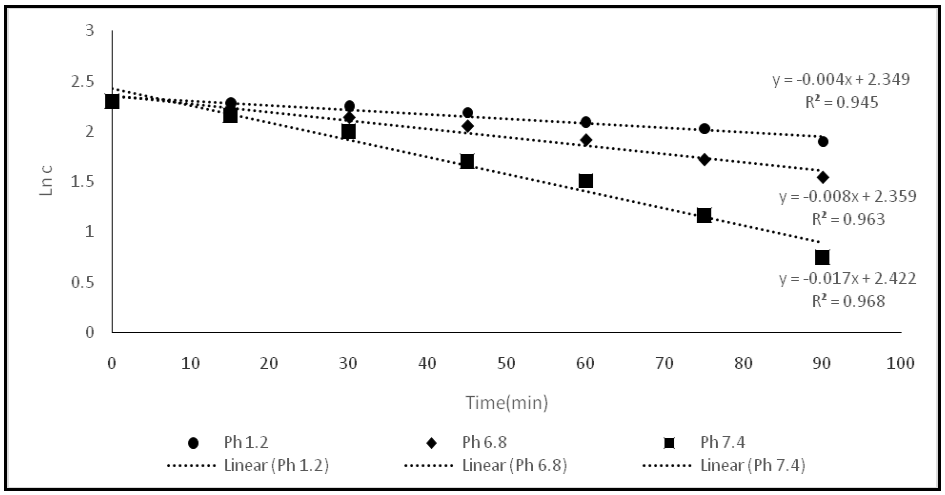


Figure 6: The hydrolysis rate of compound COe at different pH values.

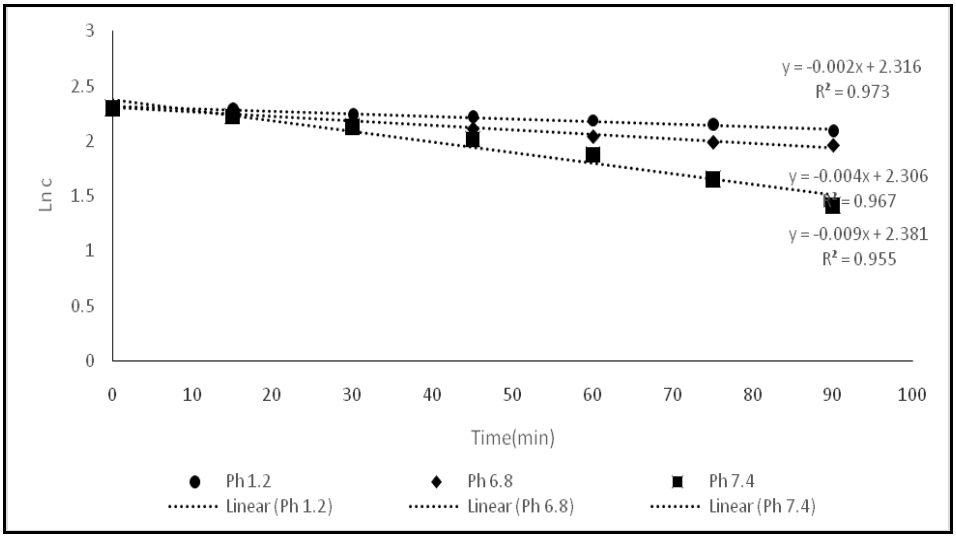


Figure 7: The hydrolysis rate of compound COf at different pH values.

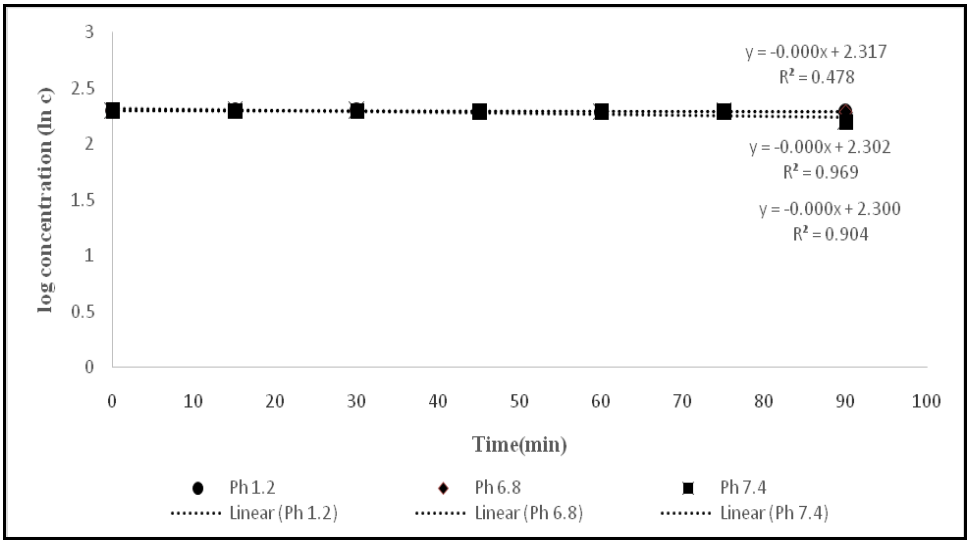


Figure 8: The hydrolysis rate of compound COg at different pH values.

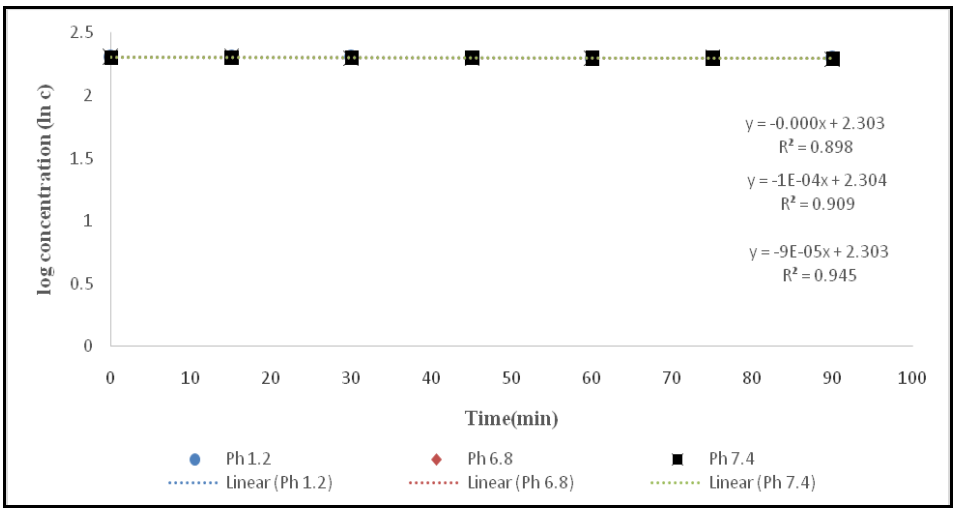


Figure 9: The hydrolysis rate of compound COh at different pH values.

3. RESULTS AND DISCUSSION

Codrugs of propranolol and metformin were prepared with an intend to increase the bioavailability of drug in a time controlled drug delivery and thereby increasing the duration of action. The schematic representation of synthesis is mentioned in **Figure 1.** In the present work phthalic anhydride and various succinic and maleic anhydride derivatives were used to prepare the prodrugs **Pa-h**. The physicochemical characterization like melting point and spectral characterization by IR, ^{1}H-NMR and mass spectral data were carried out for the synthesized prodrugs and codrugs. All the reactions were monitored using precoated TLC plates. The absence of TLC spots for starting materials and appearance of single new TLC spot at different R_f value ensured completion of the reaction. The TLC plates were visualized either by iodine vapors or by viewing in UV-visible chamber. The reaction products of all the reactions were purified initially by different workup processes to remove unreacted starting materials if any and then by recrystallization using suitable solvents. The FTIR spectra of prodrug and co-drug showed the expected bands for the characteristic groups which are present in the compounds. The formations of a various prodrugs **Pa-h** were confirmed by the disappearance of IR band at 2820.35 - 3215.49 cm^{-1} for hydroxyl [–OH] group of carboxylic acid in the IR spectra's of all prodrugs and in co-drug's it is found to a new peak of amide carbonyl group [–NH(C=O)] in the range of 1764.35-1678.21cm^{-1}.

In the ^{1}H NMR spectra, all protons were seen according to the expected integral values. The aromatic protons appeared in the range of 6.614 - 8.269 ppm. The ^{1}H NMR spectrum also supports the scheme of synthesis by the absence of peak appeared at δ value 11.578 – 13.849 ppm which corresponds to –COOH functional group indicating that the –COOH group was involved in the reaction. It was converted to amide by the formation of new peak at 8.144 - 8.578 ppm which confirms the formation of co-drugs **COa to COh** of prodrugs **Pa – Ph** and metformin. The mass spectra of compounds gave molecular ions of medium intensity and the base peak usually belonged to the corresponding ions.

The kinetic of hydrolysis of the synthesized codrugs **COa-h** were studied in aqueous buffer solutions of pH 1.2 (non enzymatic Simulated Gastric Fluid, SGF), pH 6.8 (non enzymatic Simulated Intestinal Fluid) and pH 7.4 (Simulated Plasma Fluid) at 37±5°C using HPLC. The disappearance of the tested compounds displayed hydrolysis kinetics over the investigated pH and temperature. As a general pattern, the synthesized codrugs showed relative stability in the investigated aqueous solutions and the degradation rates at pH 7.4 are slightly accelerated than those observed in SGF of pH 1.2 and SIF of pH 6.8 except **COg** and **COh**. **COa, COb, COc** and **COe** showed the more hydrolysis at pH 7.4 compared to pH 1.2 and 6.8, it indicate that the compounds containing two to four carbon atom containing chain irrespective with the saturation or unsaturation possess the maximum hydrolysis. Codrugs **COa, COb, COc** and **COe** were hydrolyzed faster at pH 7.4 when compared with **COd, f, g, h**. The codrug **COd** and **COf** showed the intermediate hydrolysis of the compounds when compared with the other codrugs, which indicate the hydrolysis of the compounds, decreases with increase in the carbon chain.

The codrugs **COg** and **COh** were not hydrolyzed at any pH condition indicating that the linker containing more than seven carbon atoms diminishes the hydrolysis of the compounds.

4. CONCLUSION

The synthesis of codrugs of propranolol and metformin was successfully effected in a rather simple and scalable scheme that consist of two steps. The chemical structures of the codrug and the intermediate were confirmed by FT-IR, ^{1}H NMR and MS analysis. Absorption bands obtained in IR and NMR spectrum confirmed the formation of amide linkage between propranolol prodrugs and metformin. Preliminary kinetic study for compounds **COa-h** revealed that compounds were chemically stable to a great extent at pH 1.2 and pH 6.8 except **Coe**, which gets hydrolyzed in this pH condition. While they shows a fast chemical hydrolysis at pH 7.4, with more hydrolysis for codrugs **COa, COb, COc** and **COe** and the remaining compounds were more stable relatively. It implies that codrugs may pass unhydrolyzed through stomach and posses enough stability to be absorbed from intestine. pH specific hydrolysis and slower hydrolysis of certain codrugs indicates the rate-controlled and time controlled drug delivery of the actives. It also translates in an increase in the duration of action, increase in the efficacy of drug. As the codrugs were stable at pH 1.2 and 6.8 this indicates towards avoiding the first pass metabolism and polypharmacy. It was found that more the number of carbons in the linkage chemical hydrolysis was slow and if the numbers of carbons are less in the linkage chemical hydrolysis were faster. Hydrolysis pattern of the best codrug indicate the release the active drugs for longer period of time. On the basis of the results obtained in this work, presence of maleate, methyl maleate, dimethyl maleate and succinate group may not appears to be suitable linker whereas ethyl maleate appears to be a good linker.

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REFERENCES

1. Lago RM, Singh PP, Nesto RW. Diabetes and hypertension. Nat Clin Pract Endocrinol Metab, 2007; 10(3): 667.
2. Okosun IS Chandra KM, Choi S, Cristman J, Dever GE, Prewitt TE. Hypertension and type 2 diabetes comorbidity in adults in the United States: risk of overall and regional adiposity. Obes Res, 2001; 9(1): 1-9.
3. Monane M, Monane S, Semla T. Optimal medication use in the elderly: key to successful aging. West J Med, 1997; 167: 233 –7.
4. Lee RD. Polypharmacy: a case report and new protocol for management. J Am Board Fam Pract, 1998; 11: 140 –4.
5. Bhatiya N, Katkar K, Ashtekar S. Formulation and evaluation of co-prodrug of flurbiprofen and methocarbamol. Asian J Pharm Sci, 2016; 11(3): 449-58.
6. Das N, Dhanawat M, Dash B, Nagarwal RC, Shrivastava SK. Co-drug: An efficient approach for drug optimization. Eur J Pharm Sci, 2010; 41: 571–88.
7. Lau WM, White AW, Gallagher SJ, Donaldson M, McNaughton G, Heard CM. Scope and limitations of the co-drug approach to topical drug delivery. Curr Pharm Des, 2008; 14(8): 794–802.
8. Menger FM, Rourk MJ, Synthesis and reactivity of 5-fluorouracil/ cytarabine mutual prodrugs. J Org Chem, 1997; 62(26): 9083–8.
9. Sriram D, Yogeeswari P, Gopal G. Synthesis, anti-HIV and antitubercular activities of lamivudine prodrugs. Eur J Med Chem, 2005; 40(12): 1373–6.
10. Hideaki F, Akio W, Toru N, Minoru N, Kan M, Atsushi N, et al., Synthesis of novel twin drug consisting 8-oxaendoethanotetrahydromorphides with a 1, 4-dioxane spacer and its pharmacological activities: l, j and putative e opioid receptor antagonists. Bioorg Med Chem Lett, 2009; 19(2): 438–41.
11. Wermuth CG. The Practice of Medicinal Chemistry. In: Wermuth, C.G. (Ed.), Homo and Heterodimer Ligands: The Twin Drug Approach. Academic Press, California, 2008; 380–383.
12. Amjad MQ, Meriem MR, Bassam MT. Synthesis, characterization and in vitro hydrolysis of a gemfibrozil-nicotinic acid codrug for improvement

of lipid profile. Eur J Pharm Sci, 2011; 43(3): 99–108.
13. Krishna CC, Hitesh KA, Anil K, Keykavous P, Reza M. Synthesis, analysis, in vitro characterization and in vivo disposition of a lamivudine–dextran conjugate for selective antiviral delivery to the liver. Bioconjug. Chem, 2007; 18(6): 2097–108.
14. Cavalli A, Bolognesi ML, Minarini A, Rosini M, Tumiatti V, Recanatini M, et al., Multi-target-directed ligands to combat neurodegenerative diseases. J Med Chem, 2008; 51: 347–72.
15. Rasheed A, Lathika G, Raju Prasanna Y, Mansoor KP, Azeem AK, Balan N. Synthesis and pharmacological evaluation of mutual prodrugs of aceclofenac with quercetin, vanillin and $_{L}$-tryptophan as gastrosparing NSAIDs. Med Chem Res, 2016; 25: 70-82.
16. Brown GR, Clarke DS, Faull AW, Foubister AJ, Smithers MJ. Design of dual acting thromboxane antagonist-synthase inhibitors by a mutual prodrug approach. Bioorg Med Chem Lett, 1996; 6(3): 273-8.
17. Vigroux A, Bergon M. Synthesis of prodrug and a mutual prodrug of chlorzoxazone and acetaminophen based on a masked benzoxazolone. Bioorg Med Chem Lett, 1995; 5(5): 427-30.
18. Nielsenw NW, Bundgaard H. Glycolamide esters as biolabile prodrugs of carboxylic acid agents: synthesis, stability, bioconversion and physicochemical properties. J Pharm Sci, 1988; 77: 285–98.