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DESIGN AND SYNTHESIS OF A NOVEL PYRAZOLO[3,4-*B*]QUINOLINYL ACETOHYDRAZIDE AND SCHIFF BASE DERIVATIVES

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ABSTRACT
A novel series of pyrazolo[3,4-*b*]quinolinyl acetohydrazide and Schiff base derivatives were prepared via various regents started from the key-intermediate 2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetohydrazide **9**. most of the novel-prepared compounds have been elucidated using spectroscopic analyses (NMR, and EI-MS).

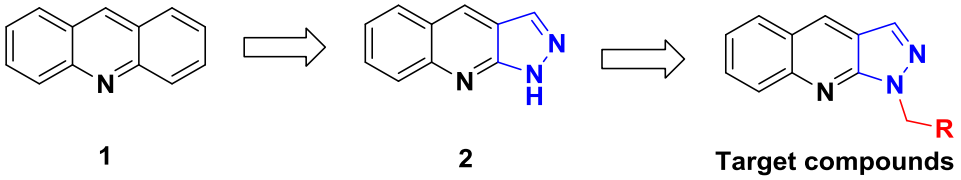
KEYWORDS: Pyrazolo[3,4-*b*]quinolone, Quninoline, pyrazolo, Schiff base, Synthesis.

INTRODUCTION

pyrazolo[3,4-*b*]quinolone is a heterocyclic fused-aromatic compound It consists of a quinoline moiety annulated with a pyrazole residue. This scaffold became a much interested compound with the importance of its role in the disease treatment.[1-12] Its derivatives have been reported for a variety of biological activities and were used in clinical uses, for example anti-microbial agents[4-7], anti-viral[1], anti-cancer activities,[13] and anti-malarial agents.[9]

The small-molecule approach presents an enormous potential for treating Cancer. In this context, several projects and strategies have been proposed for the treatment of Cancer. 9-anilinoacridine derivative (**1**, Fig. 1) was proposed as antitumor agents targeting DNA-Topoisomerase II.[14] unfortunately, the most of these derivatives show a low of selectivity towards Cancer cells, moreover the resistance problems via a range of mechanisms. Further investigation of this scaffold were therefore needed, in order to develop potent and selective compound. Synthesis of novel compounds having a bioisosteric replacement of the benzene moiety in the acridine nucleus have been done and leads to cytotoxic novel compounds, such as pyrazolo[3,4-*b*]quinolone **2**.[15]

As a further step, optimization of scaffold **2** was performed taking into account structure-activity relationships analysis and variables such as target selectivity, and ease of chemical synthesis. There were several positions that were investigated for structure-activity relationships.[13,16-18] Our target was regard to N1 position, a substituent is indeed necessary, in particular a first synthesis was performed on compounds substituted on N1 with acetohydrazide residue followed by Schiff bases derivatives (**Target compounds**, Fig. 1).

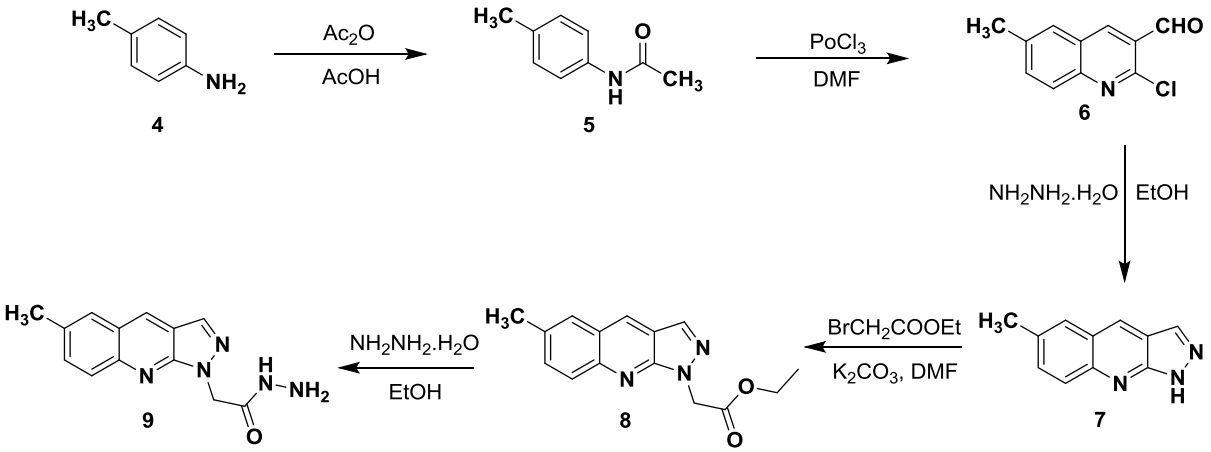


1 **2** **Target compounds**

RESULTS AND DISSCUSSION

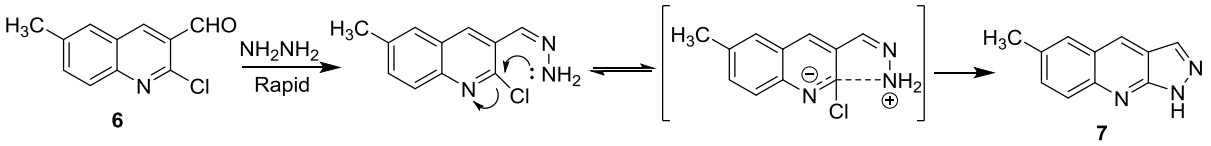
As we mentioned before, the aim of this study focused on the synthesis of novel derivatives bearing different substituents on the N1 position. And in order to get the desired target compounds, the compound 2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetohydrazide (**9**) seems to be the most suitable intermediate to start from. As seen in scheme 1, the commercially available compound *p*-toluidine (**4**) underwent acetylation in acidic conditions to give *N*-(*p*-tolyl)acetamide (**5**). Subsequently, 2-chloro, 3-formyl pyridine ring formation was a chivied by a Vilsmeier-Haack-formylation reaction, using phosphorous oxychloride ($POCl_3$) and *N*,*N*-Dimethylformamide (DMF), leading to compound 2-chloro-6-methylquinoline-3-carbaldehyde (**6**). There are a number of methods available for the synthesis of

pyrazolo[3,4-*b*]quinolone scaffold.[17] The most efficient and commonly used involves, the formation of hydrazone via the reaction of the formyl group with the hydrazine, followed by cyclization by attack of hydrazone on the carbon bearing a chlorine atom to afford 6-methyl-1*H*-pyrazolo[3,4-*b*]quinolone (**7**).



Scheme 1: Synthesis of the key-intermediate 9.

Subsequently, alkylation reaction of **7** with ethyl bromoacetate in the presence of potassium carbonate to afford the desired product, ethyl 2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl) acetate **8**. The latter product underwent a hydrazinolysis reaction with hydrazine hydrate in order to obtain the key-intermediate 2-(6-methyl-1*H*-pyrazolo[3,4-*b*] quinolin-1-yl) acetohydrazide **9** (Scheme 1).

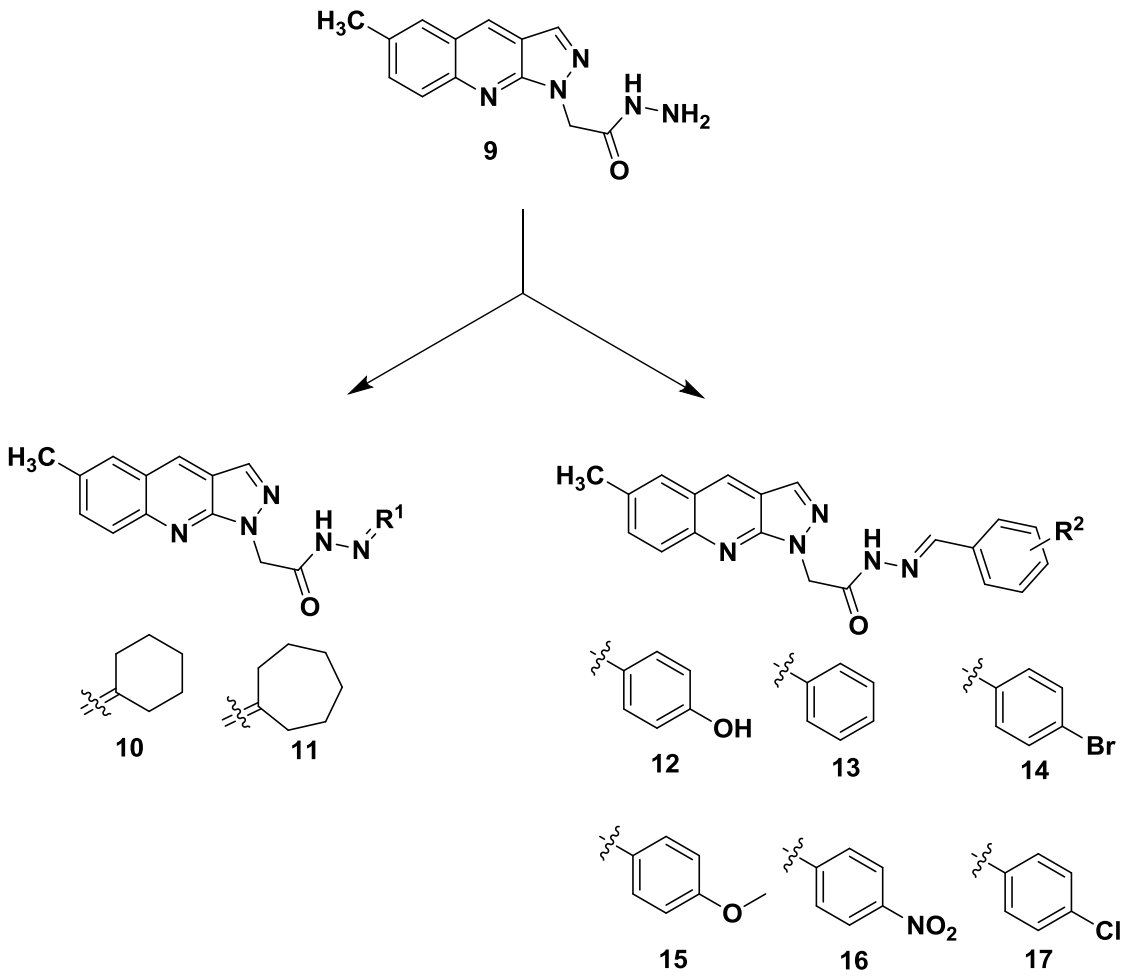


Scheme 2: Reaction mechanism of the formation of pyrazolo[3,4-*b*]quinolone.

The structure of the prepared derivatives was elucidated using mass spectrometry, ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H NMR of compound **8** indicated the disappearance of singlet signal for NH group. Moreover, appearance of new aliphatic protons at 5.40 ppm (CH_2), and 1.20 & 4.19 ppm for (CH_2CH_3). The structure of compound **9** was established by ^{1}H NMR, in which the signals corresponding to $COOCH_2CH_3$ in compound **8** were replaced by signals attributable to the new $NHNH_2$ group at 4.20 and 13.50 ppm.

Schiff bases are well-known compounds and have been reported to have several biological activities.[19-21] These compounds formed by a condensation reaction between the primary amines or analogues for example (hydrazone and hydrazine derivatives) and aldehydes. In addition, the aromatic primary amine derivative having different substituents donor or withdrawing which help to study the structure-activity relationships and that leads to enhancing and regulating the biological activities. Construction of the Schiff base derivatives by the condensation of the acetohydrazide **9** and the appropriate aldehyde/ketone affording the corresponding benzylidene derivatives **10**-**17**.

The structure of the novel Schiff bases derivatives **12**-**17** was confirmed by mass spectrometry, ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H NMR indicated the disappearance of peaks at 4.2 ppm (NH_2) and the appearance of a singlet signals corresponding to the new (-CH=N) proton, as well as the appearance of new aromatic protons (C6H5). The details of the spectroscopy characterization data of the synthesized compounds are incorporated in the experimental part.



Scheme 3: Synthesis of the target compounds 10-17.

CONCLUSION

In conclusion, a novel series of *N1*- substituted pyrazolo[3,4-*b*]quinolinyl acetohydrazide and Schiff base derivatives were designed and synthesized via a practical and mild method started from the key-intermediate 2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetohydrazide **9.** The structure of the novel derivatives has been confirmed using different spectroscopic techniques (NMR spectra and EI-MS). In future reports we shall describe the evaluation of these derivatives for their *in vitro* anti-cancer activities and subsequently identified a hit compound for further modifications to synthesized more active derivatives.

Experimental

Solvents and reagents were obtained from Acros (Geel, Belgium), Fluka (Taufkirchen, Germany) or Sigma (Steinheim, Germany). All melting points were measured on a Melting Point Apparatus (Stuart Scientific, Stone, Stafford shire, UK) and were uncorrected. The NMR Spectra were recorded at 270 MHz on a Varian Mercury VX-300 NMR spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) were run in deuterated dimethylsulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass Spectra were recorded on a GC MS-QP 1000 EX Mass Spectrometer (Shimadzu, Tokyo, Japan). All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F254, Merck).

N-(*p*-tolyl)acetamide (5, $C_9H_{11}NO$)

Equal volumes of acetic anhydride (50.00 ml) and glacial acetic acid (50.00 ml) were added to *p*-toluidene (50.00g), the reaction mixture was refluxed and boiled gently for 60 min. The mixture was poured into crushed ice and the resulting solid filtered off, washed with water, dried to afford **5** in yield (55.00 g, 79.00%); m.p. (55-58 ^{o}C).

2,6-dimethylquinoline-3-carbaldehyde (6, $C_{11}H_8NOCl$)

To a stirred solution of **5** (7.50 g, 50.00 mmol) in dry DMF (9.60 ml, 131.50 mmol) at 0-5 ^{o}C, $POCl_3$ (32.20 ml, 237.90 mmol) was added drop wise and the mixture stirred at 80-90 ^{o}C for 48 h. The mixture was poured into crushed ice, stirred for 5 min and the resulting solid filtered, washed well with water and dried to afford **6** in yield (3.00 g, 29.00%); m.p. (110-112 ^{o}C).

6-methyl-1*H*-pyrazolo[3,4-*b*]quinolone (7, $C_{11}H_9N_3$)

A mixture of **6** (1.00 g, 4.87 mmole) and hydrazine hydrate (10.00 ml) and suitable amount of ethanol was refluxed for 8 h. The reaction mixture was cooled, to

afford a dark orange precipitate. The resulting precipitate was filtered off, washed with ethanol, and dried well to afford **7** in yield (0.60g, 67%); m.p. (145-147 ºC).

Ethyl 2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetate (8, $C_{15}H_{15}N_3O_2$)

A mixture of pyrazoloquinoline (0.50 g, 2.70 mmol) and K_2CO_3 (0.37 g, 2.70 mmol) in suitable amount DMF, and ethyle bromoacetate (0.40 g, 2.70 mmol) Stirred for 24 h at rt, poured onto ice water and the solid product was collected by filtration to give **8** in yield(0.42 g, 58.00%) as a yellow powder; m.p. (88-90 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.20 (t, 3H, CH_3CH_2), 2.5 (s, 3H, CH_3), 4.19 (q, 2 H, CH_2CH_3), 5.40 (s, 2 H, CH_2), 7.70 (d, 2H, Ar-H), 7.95 (s, 1H, Ar-H), 8.50 (s, 1H, Ar-H), 8.89 (s, 1H, pyrazole-H) ppm.

2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetohydrazide (9, $C_{13}H_{13}N_5O$)

Hydrazin hydrate (0.037g, 0.74 mmol) was added to a solution of **8** (0.20g, 0.74 mmol) in ethanol suitable amount and the result mixture was refluxed for 8 hr. The precipitated was filtered off and washed several times with hot ethanol to give **9** in yield (0.13 g ,0.72%) as a yellow powder; m.p. (187-189 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 4.2 (br.s, 2H, NH_2), 5.13 (s, 2H, CH_2), 7.64 (d, 1H, Ar-H), 7.91 (d, 1H, Ar-H), 8.43 (s, 1H, Ar-H), 8.84 (s, 1H, Ar-H), 9.34 (s, 1H, pyrazole-H), 13.50 (br, 1H, NH) ppm.

General procedure for the synthesis of 10- 17

A mixture of **5** (0.20 g, 0.78 mmol) and aldehyde or ketone (0.78 mmol) in 22.00 ml absolute ethanol in the presence of few drops of piperidine was refluxed for 8h. The formed solid was filtered off and dried. The obtained compounds were further purified by crystallized from ethanol.

***N'*-cyclohexylidene-2-(6-methyl-1*H*-pyrazolo[3,4-b]quinolin-1-yl) acetohydrazide (10, $C_{19}H_{21}N_5O$)**

Yield (0.22 g, 84.61%) as a Brown solid; m.p. (160-162°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.59 (m, 2H, CH_2), 2.42 (m, 4H, $2CH_2$), 2.43 (m, 4H, $2CH_2$), 2.5 (s, 3H, CH_3), 5.57 (s, 3H, CH_2CO), 7.65 (m, 2H, Ar-H), 7.92 (s, 1H, Ar-H), 8.44 (s, 1H, Ar-H), 8.85 (s, 1H, pyrazole-H), 10.67 (br.s, 1H, NH) ppm.; MS (EI, *m/z*, 70 eV): Calcd.= 335.17. Found= 336.23 [M^{+1}].

***N'*-cycloheptylidene-2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)aceto hydrazide (11, $C_{20}H_{23}N_5O$)**

Yield (0.11 g, 73.33%) as a white solid; m.p.(159-160°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50- 2.50 (m, 12H, $6CH_2$), 2.50 (s, 3H, CH_3), 5.55 (s, 2H, CH_2), 7.65 (m, 2H, Ar-H), 7.92 (s, 1H, Ar-H), 8.44 (s, 1H, Ar-H), 8.85 (s, 1H, pyrazole-H), 10.40 (br.s, 1H, NH) ppm.; MS (EI, *m/z*, 70 eV): Calcd.= 349.19. Found= 350.08 [M^{+1}].

(*Z*)-*N'*-(4-hydroxybenzylidene)-2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetohydrazide (12, $C_{20}H_{17}N_5O_2$)

Yield (0.21 g, 72.41%) as a white solid; m.p. (188-190°C).; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.51 (s, 3H, CH_3), 5.71 (s, 2H, CH_2), 6.81 (t, 1H, Ar-H), 6.91 (m, 1H, Ar-H), 7.26 (m, 1H, Ar-H), 7.55 (m, 1H, Ar-H), 7.64 (m, 1H, Ar-H), 7.67 (m, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 8.46 (s, 1H, Ar-H), 8.50 (s, 1H, pyrazole-H), 8.90 (s, 1H, N=CH), 11.56 (br.s, 1H, NH) 12.0 (br.s, 1H, OH) ppm; MS (EI, *m/z*, 70 eV): Calcd.= 359.14. Found= 360.27 [M^{+1}].

(*Z*)-*N'*-benzylidene-2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-yl)aceto hydrazide (13, $C_{20}H_{17}N_5O$)

Yield (0.16 g, 76.19%) as a white solid; m.p. (200-203°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 5.74 (s, 2H, CH_2), 7.42 (m, 2H, Ar-H), 7.64-7.72 (m, 3H, Ar-H), 7. 94 (m, 3H, Ar-H), 8.05 (s, 1H, Ar-H), 8.48 (s, 1H, pyrazole-H), 8.87 (s, 1H, N=CH), 11.85 (s, 1H, NH) ppm; MS (EI, *m/z*, 70 eV): Calcd.= 343.14. Found= 344.16 [M^{+1}].

(*Z*)-*N'*-(4-bromobenzylidene)-2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetohydrazide (14, $C_{20}H_{18}N_5OBr$)

Yield (0.24 g, 61.15%) as a white solid; m.p. (205-207°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.52(s, 3H, CH_3), 5.76 (s, 2H, CH_2), 7.36 (m, 1H, Ar-H), 7.70 (m, 2H, Ar-H), 7.93 (m, 3H, Ar-H), 8.00 (m, 1H, Ar-H), 8.47 (s, 1H, Ar-H), 8.61 (s, 1H, pyrazole-H), 8.88 (s, 1H, N=CH), 11.92 (s, 1H, NH) ppm; MS (EI, *m/z*, 70 eV): Calcd.= 421..05. Found= 422.31 [M^{+1}].

(*E*)-*N'*-(4-methoxybenzylidene)-2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetohydrazide (15, $C_{20}H_{19}N_5O_2$)

Yield (0.22 g, 68.96%) as a white solid; m.p. (177-179 °C).; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.48 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.70 (s, 2H, CH_2), 6.94 (d, 1H, Ar-H), 6.99 (d, 1H, Ar-H), 7.63 (m, 3H, Ar-H), 7.90 (s, 1H, Ar-H), 7.93 (d, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 8.44 (s, 1H, pyrazole-H), 8.83 (s, 1H, N=CH), 11.56 (br.s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.94, 48.03 ($2CH_3$), 55.27 (CH_2), 114.22, 114.29, 116.44, 124.16, 126.53, 127.42, 127.78, 127.82, 128.52, 128.71, 130.06, 132.65, 133.23, 133.35, 144.00, 146.24, 150.22, 160.70 (N=CH and Ar-C), 168.18 (C=O); MS (EI, *m/z*, 70 eV): Calcd.= 373.15. Found= 374.22 [M^{+1}].

(*E*)-2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)-*N'*-(4-nitro benzylidene) acetohydrazide (16, $C_{20}H_{16}N_6O_3$)

Yield (0.24 g, 66.66%) as a brown solid; m.p. (218-220 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.49 (s, 3H, CH_3), 5.78 (s, 2H, CH_2), 7.64 (d, 2H, Ar-H), 7.95 (m, 3H, Ar-H), 8.17 (m, 3H , Ar-H), 8.45 (s, 1H, pyrazole-H), 8.84 (s, 1H, N=CH), 12.0 (br.s, 1H, NH) ppm; MS (EI, *m/z*, 70 eV): Calcd.= 388.13. Found= 389.21 [M^{+1}].

(*E*)-*N'*-(4-chlorobenzylidene)-2-(6-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-1-yl) acetohydrazide (17, $C_{20}H_{16}N_5OCl$)

Yield (0.16 g, 66.00%) as a white solid; m.p. (202-204 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.49 (s, 3H, CH_3), 5.73 (s, 2H, CH_2), 7.43 (d, 1H, Ar-H), 7.49 (d, 1H, Ar-H), 7.64 (d, 1H, Ar-H), 7.73 (d, 2H, Ar-H), 7.90 (d, 1H, Ar-H), 7.92 (s, 2H, Ar-H), 8.03 (s, 1H, Ar-H), 8.44 (s, 1H, pyrazole-H), 8.83 (s, 1H, N=CH), 11.73 (br.s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.92 (CH_3), 48.01 (CH_2), 116.40, 116.42, 127.39, 127.77, 128.58, 128.72, 128.78, 128.85, 130.07, 132.88, 133.24, 133.41, 142.85, 146.12, 146.23, 150.21, 163.63 (N=CH and Ar-C), 168.50 (C=O); [M^+, 377] MS (EI, *m/z*, 70 eV): Calcd.= 377.10. Found= 378.23 [M^{+1}].

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