ejpmr, 2017,4(7), 850-855

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

STUDIES OF PHYSICOCHEMICAL PROPERTIES AND LIPOPHILICITY OF PYRIDAZINE DERIVATIVES: AN OVERVIEW

Massud A. S. Anwair[1]* and Anisa Elhamili[1]

[1]Department of Medicinal and Pharmaceutical Chemistry, Faculty of Pharmacy, Tripoli University – Libya.

***Corresponding Author: Massud A. S. Anwair**

Department of Medicinal and Pharmaceutical Chemistry, Faculty of Pharmacy, Tripoli University – Libya.

Article Received on 23/05/2017 **Article Revised on 13/06/2017** **Article Accepted on 01/07/2017**

ABSTRACT

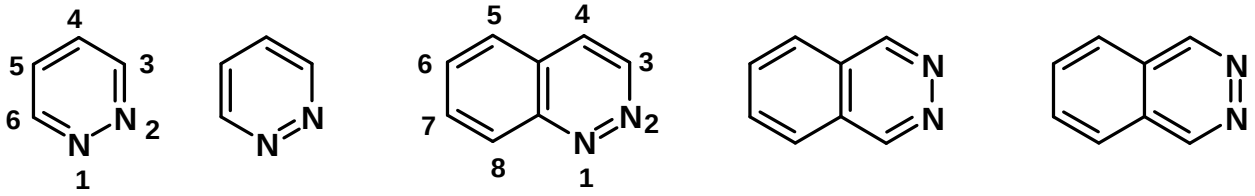
These physicochemical properties and lipophilicities review studies cover all spectroscopy methods that were used for the analysis of pyridazine derivatives structures such as calculation of N-N bond lengths, angles and electron densities. These analysis indicate the planarity and N-N single bond characteristics of these derivatives and shown no protonation or quaternization affect the bond lengths with the ring. These physicochemical properties review studies also include tautomerism, surface tension, density, melting and boiling point of many pyridazine derivatives. However, and due to the relationship between the biological activities and lipophilicities properties of these compounds, so the lipophilicity and their methods of determination were also studied. Some specific pharmacological activities such as antitumor which are related to structure activity relationship of pyridazine derivatives have also reported.

KEYWORDS: Pyridazine, tautomerism, quaternization.

INTRODUCTION

1. Physicochemical Properties

The pyridazine (1,2-diazine) **(1)** and its benzo analogs cinnolines (1,2-diazanaphthalaene or benzo[C]pyridazine **(2)** and phthalazine(benzo[d]pyridazine) **(3)** have been known since the 19th century and pyridazine is assumed to be a planar six-membered ring, existing as a resonsnce hybrid of structure **1a** and **1b** with a greater contribution from the canonical structure **1a**.[1,2,3,4,5]



1a **1b** **2** **3a** **3b**

The x-ray analysis of several pyridazine derivatives had been indicated that the pyridazine ring is planar and that protonation or quaternization does not affect the bond lengths within the ring[6,7,8,9] also, X-ray crystallographic analogs and the results of electron diffraction and microwave spectroscopy data all indicate that the N-N bond has a single bond character.[10] Other methods such as variable electronegativity - self-consistent field (VESCF), EHT, CNDO, LCAO-FE, SCMO, PPP-Cl based on a regular hexagon, energy-weighted maximum overlap (EWMO), CNDOS/S-Cl, MINDO and MINDO/2, especial in combination with photoelectron and ^{13}CNMR spectra have also been used for the calculation of N-N bond lengths, bond angles and electron densities of pyridazine.[11,12,13] In general, pyridazine is completely miscible with water and alcohols, as the lone electron pairs on the nitrogen atoms are involved in the formation of hydrogen bonds with hydroxylic solvents, benzene and ethers but it is insoluble in ligroin and cyclohexane. The solubilities of pyridazine derivatives containing OH, SH and NH_2 groups are lower than that containing alkyl groups and some physicochemical properties including melting point; boiling point; density; surface tension; pka and dipole moments that have been calculated and determine experimentally for many pyridazine derivatives containing halogen, alkyl and other groups at different positions are shown in table 1 to table 5.[14,15,16]

Table 1: Physical properties of pyridazine

Melting point	**-8 ˚*C***
Boiling point	208 ˚C (760 mm), 207.4 ˚C (762.5 mm) 87 ˚C (14 mm), 48 ˚C (1mm)
Density	d_4^{20} = 1.1054, $d_4^{23.5}$ = 1.1035, d_4^{18}=1.107
Index of refraction	$n_D^{23.5}$ = 1.5231
Surface tension	5.015×10^{10} Nm^{-2} at 0 ˚C
Salts	Hydrochloride, yellow solid, m.p. 161-163 ˚C Monopicrate, yellow solid, dec. 170-175 ˚C

Table 2: Dipole moments

	μ(D)	
Compound	**Experimental**	**Calculated**
Pyridazine	3.95	4.00
3-Methylpyridazine	3.86	3.96
4-Methylpyridazine	4.34	4.29
3-Chloropyridazine	4.42	4.24
3,6-Dichoropyridazine	4.11	3.94
3-Stylpyridazine	5.82	-
3-Acetylpyridazine	2.48	4.89[a] 2.19[b]
3-Ethoxycarbonylpyridazine	3.33	4.34[a] 2.30[b]

[a]Calculated allowing for free rotation.
[b]Calculated for *trans* configuration.

The high boiling point of pyridazine is due to intermolecular attractions, which are attributed to electrostatic forces arising from the high permanent dipole. However, the basicity of pyridazine is reduced (pka 2.33) when a second nitrogen atom is introduced into the pyridazine ring and the effects of the additional substituents on pka depend on the effect of a 2-substituents (Table 3).

Table 3: pka values for pyridazines (20°C)

Compound	***pka***	***Compound***	***pka***
Pyridazine	2.33	3-Methylmercaptopyridazine	2.26
4-Methylpyridazine	2.92	4-Methylmercaptopyridazine	3.26
3-Methoxypyridazine	2.52	3-Aminopyridazine	5.19
4-Methoxypyridazine	3.70	4-Aminopyridazine	6.69
3,6-dimethylpyridazine	1.61	3-Amino-6-methylpyridazine	5.32

The pka values are most sensitive to the effect of a 2-substituent, followed by the effects of 3- and 4-substituents; extensive sets of pka values of pyridazine derivatives have been submitted to correlation analysis, using the Hammett and the two Taft equations. The interactions between the nitrogen atom and 2-substituents account for over 70% of the inductive character and the effects of +M 4- substituents are significantly enriched in the resonance interactions, whereas –M 4-substituents interact with the nitrogen atom, mainly by induction.[16] The ring nitrogen unsubstituted pyridazines are weak acids, but maleic hydrazide is rather a strong acid. The ionization constants are given in Tables 4 and 5. Pyridazinethiones are weaker bases than the corresponding pyridazinones but methylthio derivatives are slightly weaker bases than the corresponding methoxy derivatives.

Pyridazines have attracted attention because of their easy functionalization at various ring positions, which makes them attractive synthetic building blocks for designing and developing novel pyridazine-containing agents.[31]

Some review article offers a detailed account of the design strategies employed for the synthesis of nitrogen-containing anticancer agents and other different studies describe the N-heterocyclic ring system is a core structure in many synthetic compounds exhibiting a broad range of biological activities especially antitumor when aromatic substitution on the N5 position favors the activity and this lead to increasing interest in the pyridazines, pyridazinones, pyridopyridazines, pyridopyridazinones, and their derivatives.[32, 33, 34]

Several studies were described a new method of generating the fused heterocyclic system with bridge head nitrogen pyrimido[1,2-b]pyridazinone, from 3-amino-4,5,6-triphenylpyridazine and malonic acid in presence of phosphoryl chloride and Their structures

were confirmed by their infrared, mass spectrum, ^{1}H NMR and elemental analyses.

Some studies data confirmed that the stereogenic center at C5 of the pyridazine ring plays only a marginal role in the activity and selectivity of the FPR agonists. On the other hand, the *N*-bromophenylacetamide moiety on the lactam nitrogen of the heterocyclic scaffold seems to play a major role in agonist activity, which is in agreement with previously reported agonists. Considering that pyridazine-based compounds represent good candidates for FPR-specific agonists and can activate further studies in progress to evaluate the influence of stereochemistry in other experimental *in vitro* models such as chemotaxis and neutrophils activation.[35, 36]

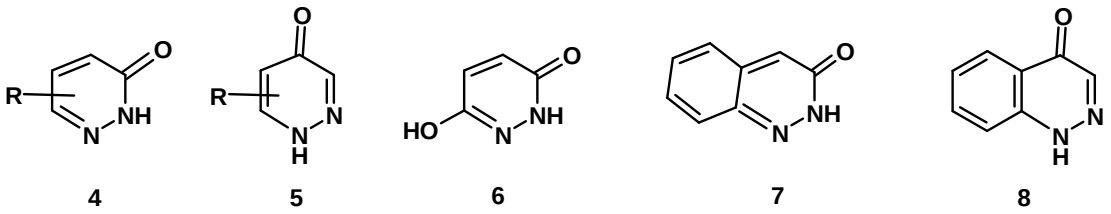
Table 4: pka values for pyridazines

Compound	Proton gain	Proton loss
Pyridazine-3(2H)-one	-1.80	10.46
Pyridazine-4(1H)-one	1.07	8.68
3-Methoxypyridazine	2.52	-
4-Methoxypyridazine	3.70	-
2-Methylpyridazine-3(2H)-one	-2.10	-
1-Methylpyridazine-4(2H)-one	1.02 1.10	- -
6-Hydroxypyridazine-3(2H)-one	5.50 5.65 5.67	13 - -
3,6-Dimethoxypyridazine	1.61	-

Table 5: pka values for sulfur-containing pyridazines

Compound	Proton gain	Proton loss	
		First	second
Pyridazine-3(2H)-thione	-2.68	8.30	-
2-Methylpyridazine-3(2H)-thione	-2.95	-	-
3-Methylmercaptopyridazine	2.26	-	-
Pyridazine-4(1H)-thione	-0.75	6.54	-
1-Methylpyridazine-4(1H)-thione	-0.83	-	-
4-Methylmercaptopyridazine	3.26	-	-
6-mercaptopyridazine-3(2H)-thione	-0.50	2.10	10.40
3,6-Bis(methylmercapto)pyridazine	-6.0	-	-
6-Hydroxypyridazine-3(2H)-thione	-1.70 -1.39	3.60 3.32	12 -
6-Methylthiopyridazine-3(2H)-thione	-	10.11	-
6-Methoxypyridazine-3(2H)-thione	-2.36 -2.30	6.95 8.50	- -
3-Methoxy-6-methylthiopyridazine	1.84	-	-
6-Aminopyridazine-3(2H)-thione	-0.14	9.05	-
6-Amino-3-methylthiopyridazine	5.61	-	-
6-Methylaminopyridazine-3(2H)-thione	-0.04	9.46	-
3-Methylthio-6-methylaminopyridazine	5.94	-	-
6- Piperidinopyridazine-3(2H)-thione	-0.06	9.31	-
3-Methyl-6-- Piperidinopyridazine	5.13	-	-

Many studies on the tautomerism of pyridazine with potentially tautomeric groups such as prototropic tautomerism of pyridazines with a hydroxyl group at an α or γ position relative to a ring nitrogen atom are illustrated by fig. 1. The studies show that 3- and 4-hydroxypyridazines of pyridazines compounds (4) and (5) exist predominantly in the oxo form, while maleic hydrazide and substituted maleic hyrazides exist in the monohydroxymonooxo compound form (6). Similarly, 3- and 4-hydroxycinnolines and their derivatives exist predomintly in the oxo forms compounds (7) and (8). The phthalazin-4-ones exist in the oxo form and phthalic hydrizide in the monohydroxymonooxo form compound (9), while 4- and 6-hydroxypyridazine-1-oxides exist predomintly in the N-hydroxypyridazinone forms compounds (10) and (11), while 3-and 5-hydroxypyridazine-1-oxides exist in the hydroxy N-oxide forms compounds (12) and (13).[17]



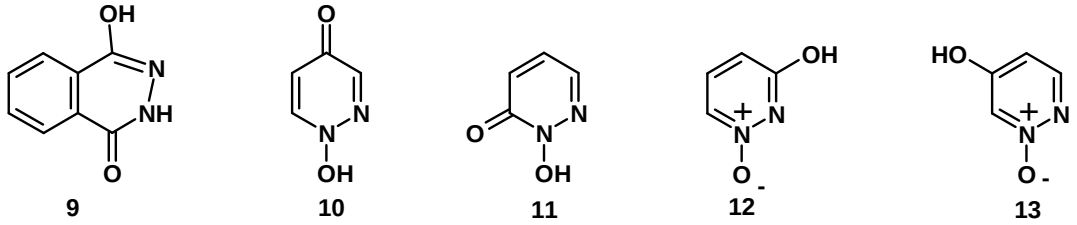


Figure 1: Tautomerism of Pyridazines with hydroxyl group

The pyridazine-3(2H)-thiones exist in the thione form compound (14) and 6-mercaptopyridazine-3(2H)-thione in monothiolmonothione form compound (15) in aqueous solution, while in the solid state 6-hydroxypyridazine-3(2H)-thiones are in the hydroxythione form compound (16) and 6-aminopyridazine-3(2H)-thiones are in the aminothione form compound (17).[18] Both 3- and 4-aminopyridazines exist in the amino form; 4-aminocinnline was formerly claimed to be anomalous and to be best represented in the imino form compound (18), while 4-alkylamino-3-phenylcinnolines are in the amino form fig. 2.

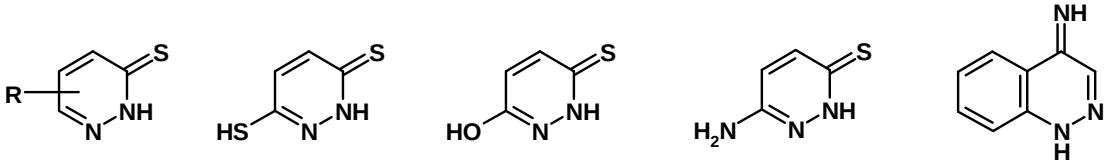


Figure 2: Tautomerism of Pyridazines with thio and amino groups

2. Lipophilicity properties

Since the demonstration of the existence of a relationship between the biological activity of a series of compounds and some simple physical properties by Overton.[19,20] lipophilicity has played an important role in research into the structure-activity relationship of drug action, which may facilitate penetration to the site of action (e. g. the brain) and the binding of the drug molecule to the receptor. These processes depend on properties of the drug molecule such as the molecular weight, configuration and other stereoelectronic properties. The lipophilicity may be a resultant of a vast array of intermolecular interactions, ranging from hydrophobic and van der waals forces to ion-dipole interactions and hydrogen bonds.[21,22,23] Generally, the lipophilicity is determined by experimental and calculation of log P according the following process:

Experimental determination of log P

This method of determination can be divided into two main classes as follows:

Direct methods

In the direct methods, one or both of the immiscible phases are analyzed quantitatively for solute. The substance to be studied by this method should be equilibrated between n-octanol and water throughout the practical range of operating conditions; no empirically fitted parameters are used in this procedure, but the direct procedures are inherently accurate. The most frequently utilized direct method techniques are:

(i) Shaking – flask method.[24]

(ii) Dual phase potentiometric titration.[25]

Indirect methods

Indirect methods are chromatographic techniques based on the empirical linear correlation between n-octanol/water partition and other partitioning phenomena; HPLC and TLC play a considerable role as alternatives of shaking-flask method, CE has also been applied for indirect log P measurement.[26,27]

Calculation of log P

There are three types of fragmental log p prediction methods:

Leo and Hansch method: Leo and Hansch and their coworkers devised a fragmental system for log P measurements which is similar to the ideas of Rekker, but uses a limited set of small molecules.[28] The general equation of Leo and Hansch as follows:

$$\log P = \sum_{j=1}^{n} aj.fj + \sum_{j=1}^{m} bj.fj$$

Where bj is a numerical factor indicating the occurrence of correction factors fj in the structure. Most of the fragments in the Leo and hansch system are single-atom, multiple-atom fundamental and multiple-atom derived fragments, together with H-polar, S-polar and ring-fused fragments. The disadvantages of this system are not as simple as that of Rekker and considerable experience is needed for correct application.

Rekker's method: Rekker and his workers introduced substituent constants to develop fragmental methods. They set out from a large set of experimental log p values which extended to more than 1000 compounds. They calculated the log P of a compound by adding the fj values of its fragments.

$$\text{Log } P = f_R + f_X$$

then generalized to $\log P = \sum_{j=1}^{n} aj.fj$,

Where aj is a numerical factor indicating the occurrence of fragment fj in the structure.

The important condition of fragmental systems is that the calculation of log P values must be independent of the extent and mode of fragmentation. Finally, Rekker derived correction factors based on his magic constant(C_M) and gave the complete equation of the Rekker fragmental system as follows:

$$\log P = \sum_{j=1}^{n} aj.fj + \sum_{j=1}^{m} kn;C_M$$

This system has the advantage of simplicity, ease of use and versatility.[29]

System of atomic contribution

This system was developed by Moreau and colleagues, based on the concept that log P is made up of atomic contributions, which vary, however, with the atomic enviroment. They derived a set of 222 substructures from a set of 1868 compunds with known P_{oct} values, which they called the "contribution" set; each substructure defines a particular atomic environment.[30]

3. CONCLUSION

The important of this overview of the physicochemical and lipophilicity of pyridazine derivatives to promote and activate research workers to synthesize a large number of these derivatives because of interest discovery that of several pyridazine derivatives possess characteristic pharmacological and biological activities and to search the promising pharmacological active compounds. Also, we indicate for important role of lipophilicity in structure-activity relationships, and how to facilitate penetration of the drug to the site of action and binding of the drug molecule to the receptor. However, these penetration processes depend on the structural properties of the drug molecule, such as molecular weight; configuration and other stereoelectronic properties. Also, the lipophilicity may depend on a vast array of intermolecular interactions, ranging from hydrophobic and van der waals forces to ion-dipole interactions and hydrogen bonds.

REFERENCES

1. T. L. Jacobs, in ´Heterocyclic Compounds´, ed. R. C. Elderfield, Wiley, New York. vol. 1957; 6: 101.
2. G. R. Ramage and J. K. Landquist, in Rodd´s Chemistry of Carbon Compounds, ed. S. Coffey, Elsevier, Amsterdam, 1959; IV: 1217.
3. J. C. E. Simpson, Chem. Heterocycl. Compd. 1953; 5: 69.
4. O. Büyükgüngör and M Odabasoglu K, 2-(2-Hydroxyethyl)phthalazin-1(2H)-one, Acta Cryst. 2008; 6: 756.
5. G. Dutkiewicz, C. S. Chidan Kumar, H. S. Yathirajan, A. N. Mayekar and M. Kubicki, 3-Methyl-1,2,4-triazolo[3,4-a]phthalazine monohydrate, Acta Cryst. 2009; 65: 2694.
6. O. Büyükgüngör, M Odabasoglu, B. Narayana, A. M. Vijesh and H. S. Yathirajan, Phthalazin-1(2H)-one, Acta Crystallogr. 2007; 63: 3198.
7. P. Cuka; Acta Crystallog. 1963; 16: 318.
8. L.M. C. Vieira, A. M. Fonseca, M. M. Raposo and G. Kirsch, Electrochemical and Spectroscopic Studies of Pyridazine Derivatives, Portugaliae Electrochimica Acta. 2004; 22: 11-18.
9. B. J. Graves, D. J. Hodgson, S. F. Chen and R. P. Panzica, Heterocycles, 1981; 16: 9.
10. Almenningen, G. Bjornsen, T. Ottersen, R. Seip and T. G. Strand, Acta Chem. Scand., Ser. A. 1977; 31: 63.
11. R. N. Castle, Chem. Heterocycl. Comp. 1973; 28: 1.
12. E. W. Thulstrup, J. Spanget-Larsen and R. Gleiter, Mol. Phys, 1979; 37: 1381.
13. R. Alfini, M. Cecchi and D. Giomi, Reactivity and Synthetic Application of 4,5-Dicyanop, Molecules, 2010; 15(3): 1722-1745.
14. T. L. Jacobs, in ´Heterocyclic Compounds´, ed. R. C. Elderfield, Wiley, New York. 1957; 6: 136.
15. R. G. Ramage and J. K. Landquist, ed. S. Coffey; Elsevier, Amsterdam, 1959; IV: 1201.
16. P. Tomasik and R. R. Zalewski, Chem. Zvesti, 1977; 31: 246 (CA 88, 1978, 135 982.).
17. R. Katritzky and J. M. Lagowski, Adv. Heterocycl. Chem. 1963; 1: 339.
18. M. Tisler and B. Stanovnik, Chem. Heterocycl. Compd. 1973; 28: 755.
19. C. E. Overton, Studien über die Narkose, zugleich ein Beitrag zur allgemeinen Pharmakologie, G Fischer, Jena, 1901.
20. L. Kārolyhāzy, M. Frelle, M. A. S. Anwair, G. Beke, F. Glannini, M. V. Castelli, M. Sortino, J. C. Ribas, S. Zacchino, P. Mātyus and R. D. Enriz, Synthesis, in Vitro/ in Vivo Antifungal Evaluation and Structure-Activity Relationship Study of 3(2H)-

pyridazinones, Arzneim.Forsch. Drug Res., 2003; 53(10): 738-743.
21. M. A. S. Anwair, L. Kārolyhāzy, D. Szabö, B. Balogh, I. Kövesdi, V. harmat, J. Krenyācz, Ă. Gellērt, K. Takācs-Novāk and P. Mātyus, Lipophilicity of Aminopyridazinone Regioisomers, Journal of Agricultural and food chemistry, 2003; 51(18): 5262-5270.
22. H. Vander de Waterbeemd and B. Testa, The parameterization of lipophilicity and other structural properties in drug design,. In Advances in Drug Research, vol 16. Testa B. (Ed). Academic Press, London, 1986; 85.
23. L. Kārolyhāzy, D. Szabö, M. A. S. Anwair, A. P. Borosy, K. Takācs-Novāk and P. Mātyus, Lipophilicity of Regioisomers: a case study on 3(2H)-pyridazinones, Journal of Molecular Structure (Theochem), 2002; 578: 89-91.
24. J. C. Deardenen and G. M. Bresnen, Quant. Struct. Act. Relat, 1988; 7: 133.
25. Hersey, A. P. Hill, R. M. Hyde and D. J. Livingstone, Quant. Struct. Act. Relat, 1989; 8: 288.
26. S. Julia and A. Ginebreda. An. Quim. 1979; 75: 346.
27. M. Chessels, D. W. Hawker and D. W. Connell, Chemosphere, 1991; 22: 1175.
28. C. Hansch and A. Leo, Substituent Constants Correlation Analysis In Chemistry And Biology, Wiley. Inter Sci, New York, 1979.
29. R. F. Rekker and H. M. Dekort, Eur. J. Med. Chem, 1979; 14: 479.
30. P. Broto, G. Moreou and C. Vandycke, Eur. J. Med. Chem. Chim. Ther., 1984; 19: 71.
31. E. M. Flefel , W.A. Tantawy , W.I. El-Sofany ,M. El-Shahat , A. A. El-Sayed and D.N. Abd-Elshafy , Synthesis of Some New Pyridazine Derivatives for Anti-HAV Evaluation, *Molecules*, 2017; *22*(1): 148.
32. K. A. Abdellatif , E. A. Abdelall , M. A. Abdelgawad , R. R. Ahmed and R. B. Bakr, Synthesis and Anticancer Activity of Some New Pyrazolo[3,4-*d*]pyrimidin-4-one Derivatives, Molecules, 2014; 19(3): 3297-3309.
33. M. Asif, Biological Potential and Chemical Properties of Pyridine and Piperidine Fused Pyridazine Compounds: Pyridopyridazine a Versatile Nucleus, Asian Journal of Chemistry and Pharmaceutical Sciences, 2016; 1(1): 29-35.
34. J. Akhtar, A. A. Khan,Z. Ali, R. Haider, M. Shahar Yar, Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities, European Journal of Medicinal Chemistry, 2017; 125: 143-189.
35. A. Deeb, F.A. El-Mariah, H.K. Abd El-Mawgoud, Pyridazine and its related compounds: Part 38. Pyrimido[1,2-b]pyridazinone, synthesis and some reactions, European Journal of Chemistry, 2015; 6(2): 204-210.
36. Cilibrizzi, L. Crocetti, M.P. Giovannoni, A. Graziano,[1]C. Vergelli, G. Bartolucci, G. Soldani, Mark T. Quinn, I. A. Schepetkin and C. Faggi, Synthesis, HPLC Enantioresolution, and X-ray Analysis of a New Series of C5-methyl Pyridazines as *N*-Formyl Peptide Receptor (FPR) Agonists, Chirality, 2013; 25(7): 400–408.