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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, anti-inflammatory activity, and QSAR study of some Schiff bases derived from 5-mercapto-3-(4′-pyridyl)-4*H*-1,2,4-triazol-4-yl-thiosemicarbazide

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Abstract The purpose of this research is to synthesize better anti-inflammatory compounds derived from 5-mercapto-3-(4′-pyridyl)-4*H*-1,2,4-triazol-4-yl-thiosemicarbazide (**5**). 2-Substituted-N-[3-(pyridin-4-yl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]hydrazine carbothioamide derivatives (**6a–j**)/(**7a–e**) are synthesized by the condensation of **5** with variously substituted aromatic aldehydes/1*H*-indole-2,3-diones, respectively, under conventional and microwave irradiation methods. The microwave method is found to be superior with higher chemical yields, tremendous reduction in time, and is environmentally benign as compared to conventional heating method. The chemical structures of the newly synthesized compounds (**6/7**) have been confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra and have been evaluated for anti-inflammatory activity by carrageenan-induced acute paw edema method in rats.

Keywords Schiff bases · Triazoles · Anti-inflammatory · QSAR · Microwave irradiation

Introduction

Heterocycles have contributed to the development of society from a biological and industrial point of view as well as to improve the quality of life. In the family of heterocyclic compounds, nitrogen containing heterocycles are frequently found in privileged structures and have played an important role in medicinal chemistry. Pyridine derivatives are potential and proven source of pharmaceuticals and agrochemicals, for the treatment of Alzheimer's disease (Davis *et al.*, 1996), agonists at 5-HT1A receptors (Vacher *et al.*, 1998), Mycobacterium tuberculosis H37Rv[3] (Gezginci *et al.*, 2001), calcium channel agonist–antagonist modulation activities (Shan *et al.*, 2002), sodium channel inhibitors (Shao *et al.*, 2004), neuronal nicotinic acetylcholine receptors (Wei *et al.*, 2005), and so on.

The search for new antimicrobial agent is one of the most challenging tasks to the medicinal chemist. The synthesis of high nitrogen containing heterocyclic system has been attracting increasing interest because of their utility in various applications such as propellants, explosives, pyrotechnics, and especially chemotherapy. The widespread use of 1,2,4-triazoles as a scaffold in medicinal chemistry established this moiety as a member of the privileged structures class. Literature survey reveals that 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically interesting drug candidates including antifungal (Papaqkonstantinon-Garoufalias *et al.*, 2002), insecticidal (Ghorab *et al.*, 1996), antibacterial (Patel *et al.*, 2010), anti-inflammatory (Labanauskas *et al.*, 2004), antitubercular (Foroumadi *et al.*, 2003), anticonvulsants (Mahendra *et al.*, 2007), H1/H2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, antianxiety agents, and sedatives (Schreier, 1976). The most important use, however, is as antimycotics in drugs such as fluconazole, itraconazole, and voriconazole (Haber, 2001).

During the past few decades, interest has been rapidly growing in gaining insight into the properties and

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transformations of these heterocycles. As a result, variety of new compounds is being added to this field every year. Among the sulfur and nitrogen containing heterocyclic compounds, semicarbazones and thiosemicarbazones have potential pharmacological activities (Cardiaa *et al.*, 2006; Küçükgüzel *et al.*, 2006; Plech *et al.*, 2011). In recent times, microwave-assisted organic reactions have become very popular and have gained special attention due to their ecofriendly nature, safety, less reaction time, and higher yields (Polshettiwar and Varma, 2008; Gomha and Riyadh, 2009). Moreover, there are only few reports (Aniket *et al.*, 2009) available in the literature on the synthesis of mercapto-pyrido-triazol-thiosemicarbazide. Therefore, an attempt has been made to synthesize some novel Schiff bases (**6** and **7**) incorporating 1,2,4-triazole nucleus and to screen them for anti-inflammatory activity.

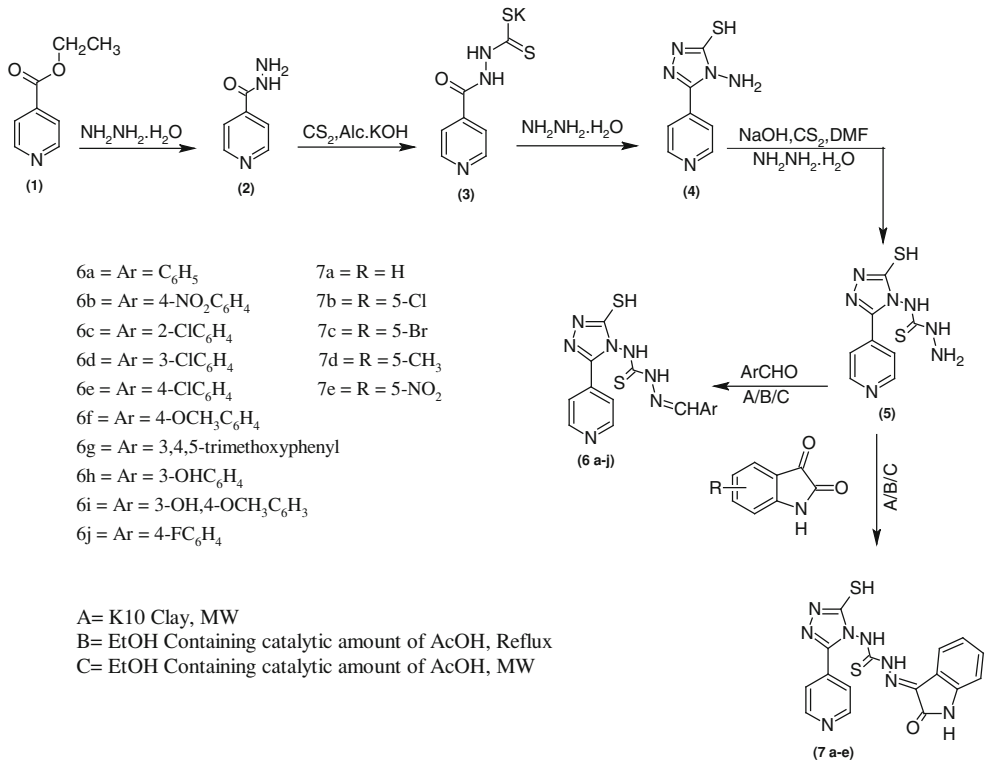
Hence, in continuation of our interest on synthesis of nitrogen containing heterocyclic compounds (Dandia *et al.*, 2001a; 2001b; 2006; Sachdeva *et al.*, 2011; Sachdeva and Dwivedi, 2012), we report herein the synthesis of novel 2-substituted-N-[3-(pyridin-4-yl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]hydrazine carbothioamide derivatives (**6a–j/7a–e**) (Scheme 1) (Tables 1, 2) by condensation of newly synthesized 5-mercapto-3-(4′-pyridyl)-4*H*-1,2,4-triazol-4-yl-thiosemicarbazide (**5**) with substituted aromatic aldehydes/1*H*-indole-2,3-diones, respectively, under conventional heating and microwave irradiation. The structures of the synthesized

Table 1 Comparative results of synthesis of **6a–j** under conventional heating (Δ) and microwave irradiation (MW) methods

Entry	Ar	Time (min/h) MW/Δ	Yield (%) MW/Δ	M.P (°C)
6a	C_6H_5	43/25	90/52	260
6b	4-$NO_2C_6H_4$	30/20	88/55	235
6c	2-ClC_6H_4	38/28	85/52	280
6d	3-ClC_6H_4	40/24	84/49	272
6e	4-ClC_6H_4	38/22	84/42	292
6f	4-$OCH_3C_6H_4$	32/40	82/53	232
6g	3,4,5-trimethoxyphenyl	42/30	80/50	247
6h	3-OHC_6H_5	40/33	82/41	255
6i	3-OH, 4-$OCH_3C_6H_3$	34/25	85/42	288
6j	4-F-C_6H_4	30/22	82/42	240

Table 2 Comparative results of synthesis of **7a–e** under conventional heating (Δ) and microwave irradiation (MW) methods

Entry	*R*	Time (min/h) MW/Δ	Yield (%) MW/Δ	M.P (°C)
7a	H	20/30	82/45	160
7b	5-Cl	25/19	74/52	183
7c	5-Br	30/18	77/38	148
7d	5-CH_3	32/20	80/40	220
7e	5-NO_2	22/20	82/52	192



Scheme 1 Synthesis of 2-Substituted-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazine carbothioamide derivatives (6a–j)/(7a–e)

compounds are determined on the basis of their FTIR, ^{1}HNMR, and ^{13}C NMR spectra. Compounds have also been screened for their anti-inflammatory activity and are found to be biologically active (Figs. 1, 2).

The in vivo anti-inflammatory activity of the synthesized compounds **6b, 6c, 6e, 6g,** and **6i** was evaluated by carrageenan-induced acute paw edema in rats and indomethacin as standard. Data of anti-inflammatory activity were expressed as mean ± SD and Dunnett's test was applied to determine the significance of the difference between the control group and rats treated with the test compounds. The anti-inflammatory activity of compounds was compared with the standard showing 84.00 % inhibition of rat paw edema whereas the tested compounds showed inhibition ranging from 41.53 to 76.92 % after 5 h (Table 4). QSAR studies were undertaken using the multiple linear regression (MLR) method to determine the role of structural features that influence the observed activity of the newly synthesized compounds.

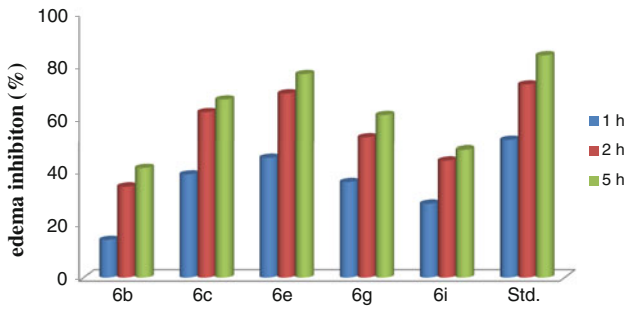


Fig. 1 Comparison of % edema inhibition shown by the test and standard compounds at 1, 2, and 5 h

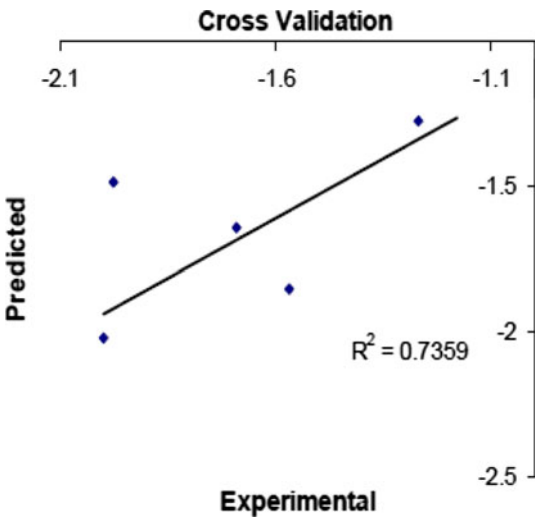


Fig. 2 *Plot* of predicted activity against experimental activity for compounds ($R^2 = 0.736$)

Results and discussion

Reaction of ethyl isonicotinate and hydrazine hydrate in absolute ethanol resulted in the formation of pyridine-4-carbohydrazide (**2**) which on treatment with CS_2 and KOH produced potassium salt of pyridine-4-carbohydrazide (**3**) in 12–18 h. Compound **3** was dissolved in water and 99 % hydrazine hydrate was added and refluxed until evolution of H_2S ceases which was checked by decolorization of the filter paper (black) when dipped in lead acetate solution and then diluted with cold water, acidified with concentrated HCl to give white solid of 5-mercapto-4-amino-3-(4′-pyridyl)-1,2,4-triazole (**4**). Compound **5** was synthesized by the reaction of **4** with NaOH and CS_2 followed by reaction with hydrazine hydrate. The reaction of **5** with substituted aromatic aldehyde/1*H*-indole-2,3-diones was carried out under conventional heating and microwave irradiation to give novel 2-substituted-N-[3-(pyridin-4-yl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]hydrazine carbothioamide derivatives (**6/7**), respectively (Scheme 1) (Tables 1, 2).

When the reaction of **5** was carried out with benzaldehyde/1*H*-indole-2,3-dione in the presence of glacial acetic acid under conventional heating, 52/45 % yield of the product 6a/7a was obtained with longer reaction time of 25/30 h, respectively. On the other hand, when compound **5** and benzaldehyde/1*H*-indole-2,3-dione were adsorbed on montmorillonite K10 clay with the help of suitable solvent and irradiated inside microwave oven, reaction was completed in 43/20 min giving 90/82 % yields of the products 6a/7a, respectively (Tables 1, 2). The products were extracted and recrystallized from ethanol. Encouraged by these results, we extended this reaction to variously substituted aromatic aldehydes/1*H*-indole-2,3-diones under similar conditions to furnish the respective Schiff bases (**6** and **7**) in good to excellent yields (74–90 %) without the formation of any side products (Tables 1, 2, 3).

The structural assignments of the newly synthesized compounds are based on spectroscopic data. IR spectrum of compound **2** shows peaks at 3,325 cm^{-1} for N–H and 1,662 cm^{-1} for carbonyl (C=O) stretching. Appearance of broad band at 3,425 cm^{-1} regarded as combination of bands due to multiple (N–H) stretching and (OH) bands (Keto-enol tautomers) shows the formation of compound **3**. The IR spectrum also shows absorptions at 1,660, 1,290, and 1,050 cm^{-1} corresponding to C=O, NH–NH, and C=S stretching vibrations, respectively. The disappearance of absorption band at 1,050 (C=S) and 1,290 (NH–NH) in **3** and appearance of band at 1,648 (C=N) in **4** due to cyclization and two peaks at 3,248 and 3,220 cm^{-1} due to asymmetric and symmetric stretching of primary amino group confirms the transformation of compound **3** into **4**. Formation of compound **5** is confirmed by the appearance of absorption band at 1,342 (C=S) cm^{-1}. Appearance of

Table 3 Infrared spectral data of the synthesized compounds (**6a–j** and **7a–e**)

Compound no.	Ar C–H stretching (in cm^{-1})	S–H stretching (in cm^{-1})	C=N stretching imine (in cm^{-1})	(–N=CH) (in cm^{-1})	(C=S) (in cm^{-1})	(C–N–C) (in cm^{-1})
6a	3,152–3,066	2,360	1,670	1,570	1,363	1,216, 1,110, 1,064
6b	3,132–3,026	2,340	1,660	1,522	1,343	1,226, 1,117, 1,054
6c	3,150–3,046	2,346	1,674	1,529	1,351	1,215, 1,113, 1,045
6d	3,124–3,016	2,344	1,658	1,512	1,360	1,217, 1,110, 1,054
6e	3,162–3,023	2,360	1,672	1,518	1,353	1,216, 1,110, 1,070
6f	3,151–3,060	2,330	1,650	1,532	1,363	1,256, 1,115, 1,064
6g	3,152–3,066	2,360	1,670	1,542	1,363	1,216, 1,110, 1,064
6h	3,142–3,046	2,350	1,663	1,523	1,361	1,226, 1,112, 1,044
6i	3,152–3,066	2,360	1,670	1,518	1,363	1,216, 1,110, 1,064
6j	3,132–3,040	2,343	1,664	1,618	1,350	1,210, 1,112, 1,044
7a	3,142–3,054	2,370	1,652	1,615	1,373	1,213, 1,132, 1,044
7b	3,152–3,083	2,332	1,662	1,620	1,362	1,216, 1,110, 1,064
7c	3,152–3,073	2,332	1,661	1,620	1,363	1,216, 1,110, 1,064
7d	3,122–3,043	2,332	1,652	1,617	1,361	1,216, 1,130, 1,051
7e	3,122–3,045	2,346	1,673	1,634	1,373	1,216, 1,110, 1,064

C=N stretching vibrations at 1,570 and 1,615 cm^{-1} shows the formation of compound **6** and **7**, respectively.

Anti-inflammatory activity

The synthesized compounds **6b, 6c, 6e, 6g,** and **6i** were evaluated for anti-inflammatory activity by carrageenan-induced acute paw edema method (Turner, 1965) in rats. Acute oral toxicity tests were performed for all the synthesized compounds as per Organization of Economic Co-operation and Development (OECD) guidelines. Statistical analysis (ANOVA followed by using Dunnett's test) was performed for anti-inflammatory activity to ascertain the significance of the exhibited activity.

The incorporation of Cl and OCH_3 groups into phenyl ring enhanced the anti-inflammatory activity of compounds considerably. Among these triazole derivatives, **6e**, **6c**, and **6g** showed significant reduction in paw edema. It was observed that the substitution at para position is more potent than at ortho and meta positions. The data obtained (Table 4) revealed that paw edema was inhibited by oral administration of the most tested compounds at a dose level of 20 mg/kg. The most active test compounds were in the decreasing order **6e > 6c > 6g > 6i > 6b** with inhibition effects ranging from 76.92 to 41.53 % compared to Indomethacin (84 %) at a dose of 10 mg/kg as standard drug.

Among the five compounds tested for anti-inflammatory activity, compounds **6e**, **6c**, and **6g** have shown significant reduction in paw edema. The compound **6e** showed the highest protection of 76.92 %, followed by compounds **6c** and **6g** showing 67.27 and 61.40 %, respectively.

The anti-inflammatory activity was performed by carrageenan-induced acute paw edema method (Turner, 1965) in rats. Albino rats of either sex, weighing between 200 and 250 g. were used in the experiment. Indomethacin 10 mg/kg was administered as standard drug. The test compounds were administered to the animals orally and after 1 h of the treatment, 0.1 ml of 1 % carrageenan suspension was injected subcutaneously in the subplantar tissue of the right hind paw and 0.1 ml of saline was injected in the subplantar tissue of the left hind paw (Winter *et al.*, 1962). Volumes of hind paws were measured using standard mercury displacement technique. Percentage change in paw volume at 0, 1, 2, and 5 h after drug administration was calculated and compared between different treatments. The percentage protection of the compounds was calculated and presented in Table 4.

QSAR study

In an attempt to determine the role of structural features that appear to influence the observed activity of the reported compounds, QSAR studies were undertaken using the multiple linear regressions (MLR) method. Several physicochemical descriptors such as hydrophobicity, topological indices, electronic parameters, and steric factors are usually used in QSAR studies in order to find the effects of different structural properties on the biological activity of compound of interest.

All variables are examined on the best model which depends on their of statistical parameters viz., Standard error of estimate (s), and sequential Fischer value (*F*), and

Table 4 Anti-inflammatory activity of the synthesized compounds

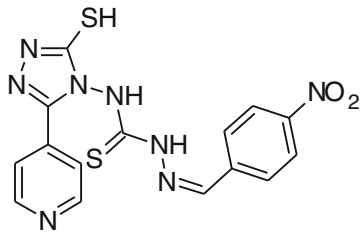
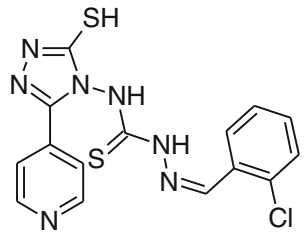
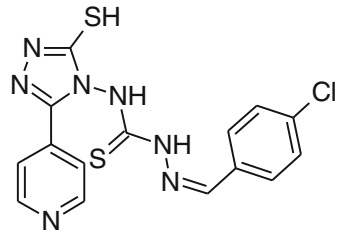
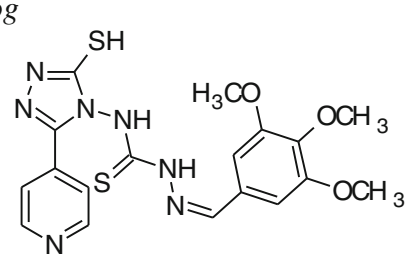
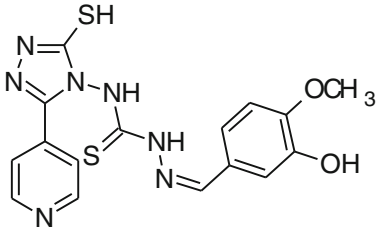
Entry	0 h	1 h	2 h	5 h
Control	0.38 ± 0.015	0.64 ± 0.010	0.78 ± 0.025	0.92 ± 0.015
6b  20mg/kg	0.41 ± 0.015	0.56 ± 0.015* 14.27 %	0.58 ± 0.025* 34.48 %	0.65 ± 0.015* 41.53 %
6c  20mg/kg	0.41 ± 0.015	0.46 ± 0.015* 39.13 %	0.48 ± 0.023** 62.50 %	0.55 ± 0.010** 67.27 %
6e  20mg/kg	0.42 ± 0.017	0.44 ± 0.025* 45.45 %	0.46 ± 0.021** 69.56 %	0.52 ± 0.015*** 76.92 %
6g  20mg/kg	0.40 ± 0.017	0.47 ± 0.015* 36.17 %	0.51 ± 0.015** 52.94 %	0.57 ± 0.015** 61.40 %

Table 4 continued

Entry	0 h	1 h	2 h	5 h
6i  20mg/kg	0.39 ± 0.015	0.50 ± 0.015* 28.00 %	0.54 ± 0.015* 44.40 %	0.62 ± 0.015* 48.38 %
Std.-indomethacin	0.40 ± 0.017	0.42 ± 0.015** 52.00 %	0.45 ± 0.021*** 73.00 %	0.50 ± 0.015*** 84.00 %

All values mean ± SD values using 5 animals in each group

Significant differences with respect to control group were evaluated by ANOVA, Dunnett's '*t*' test

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

correlation coefficient (R), were used to evaluate the obtained QASR. Acceptability of the regression model was judged by examining the correlation coefficient (R), Fischer value (F), and standard error of estimate (s), and performing multiple liner regression analysis results in statistically significant QASR models against anti-inflammatory activity.

The model when depends on only one parameter [C=N STR] or [N–CHARGE] gave ($R = 0.7{,}359$, $R = 0.7361$), respectively (Roy *et al*., 2009). The percentage of correlation coefficient (R) increases when using two parameters as shown in Eq. 1

$$\text{Model-1} = a + b \times x_1 + c \times x_2 \quad (1)$$

Model-1 shows very good correlation coefficient with ($R = 0.7359$ and $R = 0.7361$), respectively, a significant F value, and a low standard deviation, when the model depends on two parameters, as Eq. 1 model A & B; Tables 5 and 6 show the best correlation coefficient.

Since the calculated values of some electronic descriptors depend on the three-dimensional molecular geometry, the optimum 3-D geometry of the molecules were obtained by Hyperchem software (Hypercube Inc, USA), using AM1 semi-empirical method. Due to the presence of a large number of atoms in the studied molecules (at least 20 carbon and heteroatoms) semi-empirical methods were preferred over the ab initio method to save calculated time. The resulting structures were used to calculate constitutional, functional, and topological descriptors by Dragon software. Meanwhile some electronic descriptors such as frontier molecular orbital (HOMO, LUMO), dipole moment, and partial charges were calculated by the Hyperchem software. The calculated descriptors were used as independent variables in the regression analysis. The dependent

Table 5 Correlation matrix of used molecular descriptors with two parameters Eq. $1 = a + b \times x_1 + c \times x_2$

Descriptors		*R*	*S*	*F*
X_1	X_2			
C=N length	Delt gap	0.8124	1.3552	6.5502
*HOMO	C=N STR	0.7359	0.5462	61.2143
LUMO	C=N STR	0.8703	1.1239	10.7059
T.E	C=N STR	0.8542	1.2014	7.2065
Delt gap	C=N STR	0.8689	1.1095	8.9038
Charge on C-atom	C=N STR	0.8406	1.1898	7.5894
Heat formation	C=N STR	0.8325	1.1857	7.0233
C=N length	LUMO	0.8706	1.0953	10.5943
*C=N length	HOMO	0.7361	0.3213	133.5543

* Excited state of highly occupied molecular orbital

Table 6 Calculated and experimental data for the synthesized compounds

Compounds	Mp	MPC	Activity vector (log $1/k_i$)	
			Experimental	Predicted by cross validation
6b	0.73	0.38	−1.6	−1.35
6c	0.72	0.28	−1.9	−1.98
6e	0.72	0.25	−1.3	−1.52
6g	0.73	0.29	−2.3	−2.01
6i	0.68	0.32	−2.5	−1.69

Mp molecular polarizability, *MPC* maximum positive charge

variable is the activity of compounds expressed as the logarithm of reciprocal inhibition percentage [log $(1/k_i)$] (Todeschini, 2001).

The presence of co-linear descriptors may cause difficulties in certain aspects of forming a QSAR model, and hence the predictivity and generalization of a model will generally fail in the presence of highly co-linear descriptors. In order to overcome this problem, the correlation of the calculated descriptors with each other was examined and collinear descriptors ($r > 0.9$) were determined. Among these, one of them, which had the highest correlation with the dependent variable, was retained and others were removed from the data matrix.

The resulted matrix of non co-linear descriptors were used to find a multilinear equation of the form $\log(1/k_i) = b_0 + b_1DES_1 + b_2DES_2 + \cdots$ between activity and structural parameters. The stepwise selection and elimination of variables by SPSS software was used to find the best set of descriptors (Sharma *et al*., 2004; Khalafi-Nezhad *et al*., 2005; Kuramochi *et al*., 2005).

To improve the regression coefficients and attain a more predictive equation, **6b** and **6e** were considered as outliers and excluded from the model. Significant correlations were found in model using constitutional and electronic descriptors (Eqs. 2 and 3, respectively):

$$\begin{aligned} &\mathrm{Log}(1/k_i) = -23.6(\pm 4.19) + 30.11(\pm 5.27)\ \mathrm{Mp} \\ &\quad N = 10,\ R^2 = 0.77,\ \mathrm{Se} = 0.15,\ F = 27.45 \end{aligned} \tag{2}$$

$$\begin{aligned} &\mathrm{Log}(1/k_i) = 24.88(\pm 3.718) + 32.464(\pm 5.168)\ \mathrm{Mp} \\ &\quad - 1.49(\pm .0796)\ \mathrm{MPC} \\ &N = 10,\ R^2 = 0.85,\ \mathrm{Se} = 0.13,\ R^2_{cv} = 0.74,\ F = 19.77 \end{aligned} \tag{3}$$

QSAR results of the biological assay showed that all three active compounds (**6b, 6g, 6i**) belonging to nitro and methoxy group were the most active analogs. Maximum positive charge represents the maximum positive charge of atoms in a molecule ($Q_{\max} = \max\ (q^+)$) and the charge polarization is the mean absolute atomic charge in molecules defined as

$$P = \Sigma\,(|q|/A) = Q/A.$$

The presence of molecule polarizability in EQ and its direct relationship with activity vector was in accord with results obtained from structure activity relationship (SAR).

Conclusions

A novel series of Schiff bases were synthesized by conventional and microwave irradiation methods and all the compounds were characterized by spectral data. The study successfully reports synthesis of 2-substituted-N-[3-(pyridin-4-yl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]hydrazin ecarbothioamide derivatives with moderate to good yields. The microwave method is found to be superior with higher yields, tremendous reduction in time, and is environmentally benign. Among the compounds tested for anti-inflammatory activity, compounds **6e**, **6c**, and **6g** have shown significant reduction in paw edema. The compound **6e** showed the highest protection of 76.92 %, followed by compounds **6c** and **6g** which showed 67.27 and 61.40 %, respectively. With further molecular modification and manipulation of these compounds, several other promising bioactive molecules can be developed in the future.

QSAR studies clearly showed that the compounds containing nitro group are more potent than their corresponding chloro series which could be due to lower molecular polarizability values. Addition of MPC with a negative coefficient to second equation increased the correlation of the resulting equation. Since polarization can be related to two main contributors of electronic and atomic polarization, it seems that polarization, rather than electrostatic field are affecting the positive and negative charge of these two descriptors. From the results of QSAR study, it is concluded that electronic distribution is one of the most important factors in determination of activity for this group of compounds.

Experimental

General

Reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on a Toshniwal apparatus. The spectral analyses of synthesized compounds have been carried out at SAIF, IIT Madras. Purity of all compounds was checked by TLC using "G" coated glass plates and n-hexane:ethyl acetate:methanol (6:3.5:0.5) and hexane:ethyl acetate (6:4) as eluent. IR spectra were recorded in KBr on a Perkin Elmer Infrared RXI FTIR spectrophotometer, and ^{1}H NMR spectra were recorded on Bruker Avance II 500 NMR Spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard. The obtained products were identified from their spectral (^{1}H NMR, ^{13}CNMR, and IR) data. The microwave-assisted reactions were carried out in a "Catalysts Systems" Scientific Multimode MW oven attached with a magnetic stirrer and reflux condenser, operating at 700 W generating 2,450 MHz frequency.

Compounds were synthesized following the literature method (Aniket *et al*., 2009)

Synthesis of pyridine-4-carbohydrazide ***(2)***

A mixture of ethyl isonicotinate (80 gm; 0.53 mol) and hydrazine hydrate (30 gm; 29.12 ml; 0.614 mol) was refluxed in absolute ethanol (136 ml) for 6–7 h. After the completion of reaction (as monitored by TLC using hexane:ethyl acetate (6:4) as eluent), excess ethanol was distilled off. The reaction mixture was cooled to room temperature and white crystals of nicotinic acid hydrazide precipitated were filtered. Yield (%) 76 %, m.p. 168–170 °C, IR (KBr, cm^{-1}): 3,325 (NH), 3,265 (CH of pyridyl), 1,662 (CONH), 1,587 (C=N).

Synthesis of potassium salt of pyridine-4-carbohydrazide ***(3)***

To a solution of pyridine-4-carbohydrazide **(2)** in absolute ethanol (290 ml), the carbon disulfide and potassium hydroxide were added. This mixture was agitated for 12–18 h. It was then diluted with 207 ml of dry ether and the product was filtered and vacuum dried at 65–70 °C. The salts prepared as described above were obtained in nearly quantitative yields and were used without further purification.

Synthesis of 5-mercapto-4-amino-3-(4′-pyridyl)-1,2,4-triazole ***(4)***

Compound **3** (0.1 mol) was dissolved in water. To it, 99 % of 10 gm hydrazine hydrate (28.1 ml, 0.2 mol) was added. The reaction mixture was refluxed on a water bath until the evolution of H_2S gas ceased. It was then diluted with cold water (20–30 ml) and carefully acidified with concentrated hydrochloric acid. The white solid thus separated was filtered, washed with cold water, and dried and recrystallized from ethanol. TLC using hexane:ethyl acetate:methanol (6:3.5:.5) as eluent. Yield 78 %, m.p. 222–224 °C, IR (KBr, cm^{-1}) 3,220–3,248 (NH_2), 3,128 (C–N), 3,042 (–CH), 1,530 (C–N), 1,648 (C=N), 1,228, 1,110, 1,046 (C–N–C).

General procedure for synthesis of 5-mercapto-3-(4′-pyridyl)-4H-1,2,4-triazol-4-yl-thiosemicarbazide (5)

To a solution of **4** (0.01 mol, 2 gm) in DMF (10 ml) sodium hydroxide (0.015 mol, 0.62 gm) and carbon disulfide (0.015 mol, 1.12 ml) were added and the reaction mixture was stirred at 15–20 °C for 1 h. To the stirred mixture hydrazine hydrate (0.015 mol) was added and stirring was continued at 60 °C for 1 h, more on adding water, a pale white solid separated out which on recrystallization from DMF-ethanol afforded pale white crystals. Completion of reaction is checked by TLC using n-hexane:ethyl acetate as eluent. (6:4). Yield 45 % m.p. 208–210 °C, IR (KBr, cm^{-1}) 2,360 (S–H str), 1,646 (C=N str imine), 1,532 (C–N), 1,342 (C=S), 1,210, 1,110, 1,054 (C–N–C).

General microwave procedure for synthesis of Schiff bases of 5-mercapto-3-(4′-pyridyl)-4H-1,2,4-triazol-4-yl-thiosemicarbazide ***6a–6j/7a–7e***

5-Mercapto-3-(4′-pyridyl)-4*H*-1,2,4-triazole-4-yl-thiosemicarbazide **5** (1 mmol) and various aromatic aldehydes (1.5 mol)/1*H* indole-2,3-dione (1 mmol) were adsorbed on montmorillonite K10 clay with the help of suitable solvent and irradiated inside microwave oven at power 6 (420 watt, 60 %) for 20–45 min resulting in the formation of 6 and 7, respectively. The progress of reaction was monitored by TLC. Final product was extracted and re-crystallized from ethanol.

Spectroscopic characterization data of the synthesized compounds are given below:

2-Benzylidene-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazine carbothioamide ***(6a)*** ^{1}H NMR (400 MHz, DMSO): 14.53 (s, 1H, SH), 10.4 (s, 1H, NH); 8.1 (s, 1H, CH), 7.67–8.45 (m, 4H, pyridyl), 7.52–7.66 (m, 5H, Ar–H), 2.73 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 185, 164, 160, 148, 137, 126, 123, 120, 119 ppm. Anal. Calcd. for $C_{15}H_{13}N_7S_2$: C, 50.69, H, 3.69, N, 27.58. Found: C, 50.48, H, 3.67, N, 27.61.

2-(4-Nitrobenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4yl]hydrazine carbothioamide ***(6b)*** ^{1}H-NMR (400 MHz, DMSO): 14.34 (S, 1H, SH), 10.16 (S, 1H, NH); 8.41 (S, 1H, CH), 7.55–8.36 (m, 4H, pyridyl), 7.17–7.43 (m, 4H, Ar–H), 2.44 (S, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 182, 165, 158, 146, 135, 128, 123, 120, 117 ppm. Anal. Calcd. for $C_{15}H_{12}N_8O_2S_2$: C, 44.99, H, 3.02, N, 27.98. Found: C, 45.17, H, 3.00, N, 27.58.

2-(2-Chlorobenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazine carbothioamide ***(6c)*** ^{1}H-NMR (400 MHz, DMSO): 14.12 (s, 1H, SH), 10.34 (s, 1H, NH); 8.11 (s, 1H, CH), 7.35–8.25 (m, 4H, pyridyl), 7.18–7.61 (m, 4H, Ar–H), 2.5 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 182, 169, 160, 142, 135, 126, 123, 121, 115 ppm. Anal. Calcd. for $C_{15}H_{12}ClN_7S_2$: C, 46.21, H, 3.10, N, 25.15. Found: C, 46.03, H, 3.11, N, 25.12.

2-(3-Chlorobenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazine carbothioamide ***(6d)*** ^{1}H-NMR (400 MHz, DMSO): 14.24 (s, 1H, SH), 10.32 (s, 1H, NH); 8.13 (s, 1H, CH), 7.62–8.65 (m, 4H, pyridyl), 7.14–7.50 (m, 4H, Ar–H), 2.38 (s, 1H, NH) ppm. ^{13}C-NMR

(400 MHz, DMSO): 186, 166, 161, 143, 140, 131, 124, 122, 117 ppm. Anal. Calcd. for $C_{15}H_{12}ClN_7S_2$: C, 46.21, H, 3.10, N, 25.15. Found: C, 46.07, H, 3.08, N, 25.18.

2-(4-Chlorobenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazine carbothioamide ***(6e)*** ^{1}H-NMR (400 MHz, DMSO): 14.33 (s, 1H, SH), 10.4 (s, 1H, NH); 8.41 (s, 1H, CH), 7.45–8.65 (m, 4H, pyridyl), 7.10–7.50 (m, 4H, Ar–H), 2.44 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 184, 164, 160, 146, 140, 131, 124, 122, 113 ppm. Anal. Calcd. for $C_{15}H_{12}ClN_7S_2$: C, 46.21, H, 3.10, N, 25.15. Found: C, 46.59, H, 3.09, N, 25.13.

2-(4-Methoxybenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl] hydrazine carbothioamide ***(6f)*** ^{1}H-NMR (400 MHz, DMSO): 13.80 (s, 1H, SH), 10.05 (s, 1H, NH), 8.74 (s, 1H, CH), 7.62–7.99 (m, 4H, pyridyl), 6.90–7.35 (m, 4H, Ar–H), 3.81 (s, 3H, OCH_3), 2.61 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 189, 164, 160, 150, 131, 122, 114, 56 ppm. Anal. Calcd. for $C_{16}H_{15}N_7OS_2$: C, 49.85, H, 3.92, N, 25.44. Found: C, 49.33, H, 3.90, N, 25.47.

N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]-2-(3,4,5-trimethoxybenzylidene) hydrazine carbothioamide ***(6g)*** ^{1}H-NMR (400 MHz, DMSO): 13.80 (s, 1H, SH), 10.04 (s, 1H, NH), 8.80 (s, 1H, CH), 7.65–7.91 (m, 4H, pyridyl), 6.89–7.14 (m, 2H, Ar–H), 3.84–4.39 (s, 9H, OCH_3), 2.91(s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 184, 167, 162, 150, 148, 142, 130, 124, 114, 58, 56 ppm. Anal. Calcd. for $C_{18}H_{19}N_7O_3S_2$: C, 48.53, H, 4.30, N, 22.01. Found: C, 48.39, H, 4.32, N, 22.03.

2-(3-Hydroxybenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl] hydrazine carbothioamide ***(6h)*** ^{1}H-NMR (400 MHz, DMSO): 13.92 (s, 1H, SH), 9.85 (s, 1H, NH), 9.77 (s, 1H, OH), 8.1 (s, 1H, CH) 7.65–8.11 (m, 4H, pyridyl), 7.14–7.35 (m, 4H, Ar–H), 2.42 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 188, 162, 160, 148, 142, 131, 126, 121, 114 ppm. Anal. Calcd. for $C_{15}H_{13}N_7OS_2$: C, 48.50, H, 3.53, N, 26.40. Found: C, 48.35, H, 3.51, N, 26.43.

2-(3-Hydroxy-4-methoxybenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazine carbothioamide ***(6i)*** ^{1}H-NMR (400 MHz, DMSO): 13.86 (s, 1H, SH), 10.32 (s, 1H, NH); 8.1 (s, 1H, CH) 7.65-8.55 (m, 4H, pyridyl), 7.14-7.35 (m, 3H, Ar–H), 3.78 (s, 3H, OCH_3), 2.41 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 186, 165, 160, 150, 146, 132, 128, 117, 58 ppm. Anal. Calcd. for $C_{16}H_{15}N_7O_2S_2$: C, 47.87, H, 3.77, N, 24.42. Found: C, 48.06, H, 3.75, N, 24.39.

2-(4-Fluorobenzylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazine carbothioamide ***(6j)*** ^{1}H-NMR (400 MHz, DMSO): 13.62 (s, 1H, SH), 9.2 (s, 1H, NH); 8.14 (s, 1H, CH), 7.62–8.55 (m, 4H, pyridyl), 7.10–7.45 (m, 4H, Ar–H), 2.40 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 182, 167, 160, 150, 148, 131, 127, 116 ppm. Anal. Calcd. for $C_{15}H_{12}FN_7S_2$: C, 48.24, H, 3.24, N, 26.26. Found: C, 48.05, H, 3.26, N, 26.28.

2-(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazinecarbothioamide ***(7a)*** ^{1}H-NMR (400 MHz, DMSO): 14.06 (s, 1H, SH), 10.98 (s, 1H, NH, indole), 8.71 (s, 1H, NH); 8.09 (s, 1H, CH), 7.51–7.96 (m, 4H, pyridyl), 6.90–7.06 (m, 4H, Ar–H), 2.80 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 184, 167, 161, 150, 146, 138, 133, 124, 121, 117 ppm. Anal. Calcd. for $C_{16}H_{12}N_8OS_2$: C, 48.47, H, 3.05, N, 28.26. Found: C, 48.69, H, 3.03, N, 28.23.

2-(5-Chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazinecarbothioamide ***(7b)*** ^{1}H-NMR (400 MHz, DMSO): 13.44 (s, 1H, SH), 10.82 (s, 1H, NH, indole), 8.93 (s, 1H, NH); 8.11 (s, 1H, CH), 7.55–8.65 (m, 4H, pyridyl), 6.96-7.63 (m, 3H, Ar–H), 2.01 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 188, 165, 160, 151, 146, 136, 126, 120, 114 ppm. Anal. Calcd. for $C_{16}H_{11}ClN_8OS_2$: C, 44.60, H, 2.57, N, 26.00. Found: C, 44.38, H, 2.59, N, 26.03.

2-(5-Bromo-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazinecarbothioamide ***(7c)*** ^{1}H-NMR (400 MHz, DMSO): 13.52 (s, 1H, SH), 10.12 (s, 1H, NH, indole), 8.9 (s, 1H, NH); 8.12 (s, 1H, CH), 7.55–8.65 (m, 4H, pyridyl), 7.02–7.43 (m, 3H, Ar–H), 2.04 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 185, 164, 158, 148, 138, 132, 126, 121, 119 ppm. Anal. Calcd. for $C_{16}H_{11}BrN_8OS_2$: C, 40.43, H, 2.33, N, 23.57. Found: C, 40.20, H, 2.35, N, 23.55.

2-(5-Methyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazinecarbothioamide ***(7d)*** ^{1}H-NMR (400 MHz, DMSO): 13.33 (s, 1H, SH), 10.98 (s, 1H, NH, indole), 8.71 (s, 1H, NH); 8.09 (s, 1H, CH), 7.5–8.34 (m, 4H, pyridyl), 6.90-7.96 (m, 3H, Ar–H), 2.56 (s, 3H, CH_3), 2.74 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 187, 161, 150, 147, 136, 130, 127, 119, 26 ppm. Anal. Calcd. for $C_{17}H_{14}N_8OS_2$: C, 49.74, H, 3.44, N, 27.30. Found: C, 49.54, H, 3.46, N, 27.33.

2-(5-Nitro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-N-[3-(pyridin-4-yl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]hydrazinecarbothioamide ***(7e)*** ^{1}HNMR 13.42 (s, 1H, SH), 10.12 (s, 1H, NH, indole), 8.95 (s, 1H, NH); 8.11 (s, 1H,

CH), 7.65-8.49 (m, 4H, pyridyl), 6.92–7.53 (m, 3H, Ar–H), 2.08 (s, 1H, NH) ppm. ^{13}C-NMR (400 MHz, DMSO): 187, 164, 150, 146, 136, 130, 123, 118 ppm. Anal. Calcd. for $C_{16}H_{11}N_9O_3S_2$: C, 43.53, H, 2.51, N, 28.56. Found: C, 43.70, H, 2.49, N, 28.52.

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