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RESEARCH ARTICLE

Synthesis and biological evaluation of fluoropyrazolesulfonylurea and thiourea derivatives as possible antidiabetic agents

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Abstract

Fluorinated pyrazoles, benzenesulfonylurea and thiourea and their cyclic sulfonylthiourea derivatives were prepared as hypoglycemic agents. The chemistry involves the condensation of 4-hydrazino benzenesulfonamide hydrochloride with fluorochalcones to give pyrazoline derivatives which upon oxidation with bromine water afforded corresponding pyrazoles. Reaction of pyrazolines with isocyanates and isothiocyanates give the corresponding ureas and thioureas. Subsequent cyclization of these thiourea derivatives with ethyl bromoacetate and α-bromoacetophenone yielded the 4-oxothiazolidines and thiazolines, respectively. Preliminary biological screening of the prepared compounds revealed significant antidiabetic activity. Molecular and biological properties calculations revealed favorable drug-like profiles of six compounds. The structure–activity relationship (SAR) and *in silico* drug relevant properties calculations (HBD, HBA, tPSA, miLogP, molecular weight, % ABS, drug-likeness and drug score) endorse that these compounds are potential leads for future drug discovery study.

Keywords

Antidiabetic activity, benzenesulfonylureas, fluorinated pyrazoles, molecular properties calculations, thioureas

History

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Introduction

The introduction of fluorine or appropriate fluorinated functions into a molecule has become an invaluable tool for medicinal chemists[1,2]. Substitution of fluorine into a potential drug molecule not only alters the electronic environment, but it also influences the properties of neighboring functional groups. Moreover, the presence of fluorine often leads to increased lipid solubility, thereby enhancing rates of absorption and transport of drugs *in vivo*[3,4]. Therefore, there has been greater effort toward the synthesis of biologically active pyrazoles having fluorine or trifluoromethyl group as one of the substituents on either C-3 or C-5[5–7]. Furthermore, 5-aminopyrazoles and 3-trifluoromethylpyrazoles with a wide array of groups at N-1 and C-4 were reported to be selective inhibitors of cyclooxygenase[8–10] and have antidiabetic[11] properties. However, since several 3,5-dimethylpyrazoles possess hypoglycemic activities as much as 100 times that of tolbutamide in glucose-primed intact rats[12–14] studies have been conducted in our group on the synthesis of 3,5-disubstituted pyrazoles[15–20] in order to have optimum molecular scaffold for the proposed biological activity.

In continuation of our previous work on 3,5-disubstituted pyrazole[21–23] and fluorinated pyrazoles[24,25], new benzenesulfonylurea and thiourea derivatives as well as their cyclic sulfonylthioureas and 4-fluorophenyl pyrazole derivatives were synthesized and tested for hypoglycemic activity. Preliminary biological testing revealed that some compounds showed significant antidiabetic activities.

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Molecular properties such as membrane permeability and oral bioavailability are usually associated with molecular descriptors, such as partition coefficient (log *p*), molecular weight (MW) and hydrogen bond acceptors/donors. Using these descriptors, Lipinski[26] formulated a rule for drug design which states that the compounds are more likely to be drug-like and orally bioavailable if they obey the following criteria: log $p \leq 5$, molecular weight $\leq$500, hydrogen bond acceptors $\leq$10 and hydrogen bond donors $\leq$5. To further substantiate Veber et al., stated that compounds with $\leq$10 rotatable bonds and TPSA of $\leq$140 Å2 are more likely to show good bioavailability[27]. Keeping these parameters in mind, we have performed *in silico* calculations of the molecular properties of this series of compounds using online software Molinspiration[28], while the aqueous solubility, drug-likeness and drug score were calculated using the OSIRIS property explorer software[29].

Experimental

Chemistry

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and were uncorrected. The infrared (IR) spectra were recorded on Perkin-Elmer 297 infrared spectrophotometer using the plate technique. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d6 as a solvent on Bruker DPX-400-FT spectrometer using tetramethylsilane (TMS) as the internal standard. Elemental analyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University, Cairo, Egypt. Follow-up of the reactions and checking the homogeneity of the compounds were made by thin-layer chromatography (TLC) on silica gel-protected aluminum sheets (Type 60 F254, E. Merck) and the spots were detected by

exposure to UV lamp at λ 254. Biological testing was performed in the Faculty of Medicine University of Alexandria, Egypt. Reagents were of analytical grade and were used without further purification.

General procedure for the preparation of 1-fluorophenyl-3-substituted propen-1-one (Chalcones) (1a–d)

A solution of 4-fluorobenzaldehyde (1.24 g, 10 mmol) in ethanol (20 mL) was added to a stirred solution of appropriate ketone (1.12 g, 10 mmol) in ethanolic potassium hydroxide (20 mL, 20%) and stirring was maintained for 6–8 h at room temperature. The reaction mixture was then poured onto cold water (200 mL) and left overnight. The precipitated solid was collected, washed with water, dried and recrystallized from ethanol.

*3-(4-Bromophenyl)-1-(4-fluorophenyl)propen-1-one (**1a**)*

Recrystallized from ethanol as needles; (2.9 g, 96%), m.p. 140–142 °C; ν_{max} (cm^{-1}, KBr): 1644 (C=O). ^{1}H NMR (δ/ppm, DMSO-d_6): δ 7.20 (*d*, *J*= 24 Hz, 1H, *H*-α)7.78 (*d*, *J* = 24 Hz, 1H, *H*-β), 7.05–7.89 (*m*, 8H, Ar-H). ^{13}C NMR (δ/ppm, DMSO-d_6): 129.15 (*C*-α), 142.99 (*C*-β), 116.20, 121.14, 128.44, 130.23, 131.08, 131.63, 134.97, 163.82 (Ar-*C*), 187.92 (*C*=O). Anal. % Calcd for $C_{15}H_{10}BrFO$: C, 59.04; H, 3.30. Found: C, 58.92; H, 3.41.

*1-(4-Fluorophenyl)-3-(4-tolyl)propen-1-one (**1b**)*

Recrystallized from ethanol as needles; (2.3 g, 94%), m.p.134–136 °C; ν_{max} (cm^{-1}, KBr): 1648 (C=O). ^{1}H NMR (δ/ppm, DMSO-d_6): δ 2.39 (*s*, 3H, CH_3), δ 7.47 (*d*, *J* = 24 Hz, 1H, *H*-α), 7.77 (*d*, *J* = 24 Hz, 1H, *H*-β), 7.09–7.94 (*m*, 8H, Ar-H). ^{13}C NMR (δ/ppm, DMSO-d_6): 21.71 (CH_3), 129.38 (*C*-α), 143.76 (*C*-β), 116.19, 121.81, 128.65, 130.34, 131.29, 135.56, 143.09, 164.85 (Ar-*C*), 189.80 (*C*=O). Anal. % Calcd for $C_{16}H_{13}FO$: C, 79.98; H, 5.45. Found: C, 80.10; H, 5.41.

*1-(4-Fluorophenyl)-3-(2-furyll)propen-1-one (**1c**)*

Recrystallized from ethanol as needles; (1.9 g, 88%), m.p. 110–112 °C; ν_{max} (cm^{-1}, KBr): 1650 (C=O). ^{1}H NMR (δ/ppm, DMSO-d_6): δ 7.25 (*d*, *J* = 24 Hz, 1H, *H*-α), 7.80 (*d*, *J* = 24 Hz, 1H, *H*-β), 6.81–7.88 (*m*, 8H, Ar-H). ^{13}C NMR (δ/ppm, DMSO-d_6): 129.55 (*C*-α), 143.08 (*C*-β), 111.89, 112.45, 116.72, 131.43, 132.83, 145.32, 155.65, 166.02 (Ar-*C*), 188.92 (*C*=O). Anal. % Calcd for $C_{13}H_9FO_2$: C, 72.22; H, 4.20. Found: C, 72.34; H, 4.40.

*1-(4-Fluorophenyl)-3-(2-pyidyl)propen-1-one (**1d**)*

Recrystallized from ethanol as needles; (2.0 g, 89%), m.p. 98–100 °C; ν_{max} (cm^{-1}, KBr): 1646 (C=O). ^{1}H NMR (δ/ppm, DMSO-d_6): δ 7.23 (*d*, *J* = 24 Hz, 1H, *H*-α), 7.86 (*d*, *J* = 24 Hz, 1H, *H*-β), 7.10–7.87 (*m*, 8H, Ar-H). ^{13}C NMR (δ/ppm, DMSO-d_6): 129.02 (*C*-α), 146.36 (*C*-β), 121.76, 122.26, 116.75, 131.73, 132.32, 136.87, 149.08, 155.73, 167.03 (Ar-*C*), 187.2 (*C*=O). Anal. % Calcd for $C_{14}H_{10}FNO$: C, 74.00; H, 4.44; N, 6.16. Found: C, 74.21; H, 4.52; N, 6.23.

*4-[3-Aryl-5-(4-fluorophenyl)-4,5-dihydropyrazole-1-yl]benzenesulfonamide (**2** and **3**)*

A solution of the appropriate chalcone (0.02 mol) in ethanol (25 mL) was refluxed with *p*-sulfonylphenylhyrazine hydrochloride (4.9 g, 0.022 mol) for 3 h. The reaction mixture was concentrated, and the separated product was filtered, washed with cold ethanol/water (20:80) mixture and recrystallized from ethanol (Table S1).

*4-[3-Aryl-5–(4-fluorophenyl)pyrazole-1-yl]benzenesulfonamide (**4** and **5**)*

To a stirring suspension of the appropriate pyrazoline derivative (0.01 mol) in water (10 mL), 15 mL of 5% bromine water was gradually added over a period of 30 min at room temperature. After stirring for another 3 h, the pyrazole derivatives thus formed were collected by filtration, thoroughly washed with water and dried. They were recrystallized from ethanol.

*N^1-Substituted-N^3-{4-[(3-aryl-5–(4-fluorophenyl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl}urea derivatives (**6–17**)*

A mixture of the appropriate pyrazoline (10 mmol) and anhydrous K_2CO_3 (1.4 g, 10 mmol) in dry acetone (25 mL) was heated under reflux with the corresponding isocyanate (10 mmol) for 18 h. The solvent was removed *in vacuo* and the remaining solid residue was dissolved in water (30 mL). After neutralization of the resulting solution with 2N HCl, the precipitated crude product was filtered, washed with water, dried and recrystallized from a proper solvent (Table S1).

*N^1-Substituted-N^3-{4-[(3-aryl-5–(4-fluorophenyl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl}thiourea derivatives (**18–32**)*

A solution of the appropriate isothiocyanate (10 mmol) in dry acetone (5 mL) was added to a mixture of the pyrazoline (10 mmol) and anhydrous K_2CO_3 (1.4 g, 10 mmol) in dry acetone (25 mL). The resulting reaction mixture was heated under reflux for 10 h. The reaction mixture was worked up as mentioned previously for compounds **6–17**. The crude products were recrystallized from the proper solvent (Table S1).

*3-Substituted-2-[4–(5-fluorophenyl-3-substituted-4,5-dihydropyrazol-1-yl)benzenesulfonylimino]-4-oxothiazolidines (**33–37**)*

To a solution of the appropriate thiourea derivative (0.01 mol) in absolute ethanol (20 mL) was added ethyl bromoacetate (1.84 g, 0.011 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol). The reaction mixture was heated under reflux for 2 h. After cooling, the reaction mixture was poured into ice-cold water (30 mL). The solid product thus formed was filtered, washed with water, dried and recrystallized from the proper solvent (Table S1).

*3-Substituted-2-[4–(5-fluorophenyl-3-substituted-4,5-pyrazol-1-yl)benzenesulfonylimino]-thiazolines (**38** and **39**)*

A solution of the appropriate thiourea derivative (0.01 mol) in absolute ethanol (20 mL) was refluxed with phenacyl bromide (2.2 g, 0.011 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) for 3 h. During reflux, the solid product was partially separated in the reaction mixture. The mixture was allowed to attain room temperature and the solid product was filtered, washed with cold ethanol, dried and recrystallized from ethanol.

Biological evaluation

Procedure for antidiabetic activity

Compounds **2–7**, **10**, **11**, **14**, **15**, **18**, **21**, **22**, **25**, **27**, **30**, **31** and **33–39** were tested for hypoglycemic activity using alloxan-treated female albino mice weighing 20 g. Alloxan 100 mg/kg was injected into the tail vein in a 10 mg/mL saline solution (Supplementary material). Three days later, the mice were given the test compounds orally in suspension in 1% carboxymethylcellulose solution at the rate of 0.2 mmol/kg of the body weight. Each day, a group of four mice was used as a control group and one group of five mice was given the standard 100 mg of phenformin/kg. Up to six groups of four mice received the test

compounds. Blood samples were collected into 0.04% NaF solution at 0, 1 and 3 h. Glucose was determined by the microcolorimetric copper reduction technique of Haslewood and Strookman[30]. Results are expressed as a percentage reduction of the plasma glucose levels compared to the control value. Statistical significance was assessed by Student's *t*-test. Statistical significance was accepted where the calculated *t*-value exceeded the tabulated *t*-value at the $p = 0.05$ level.

Results and discussion

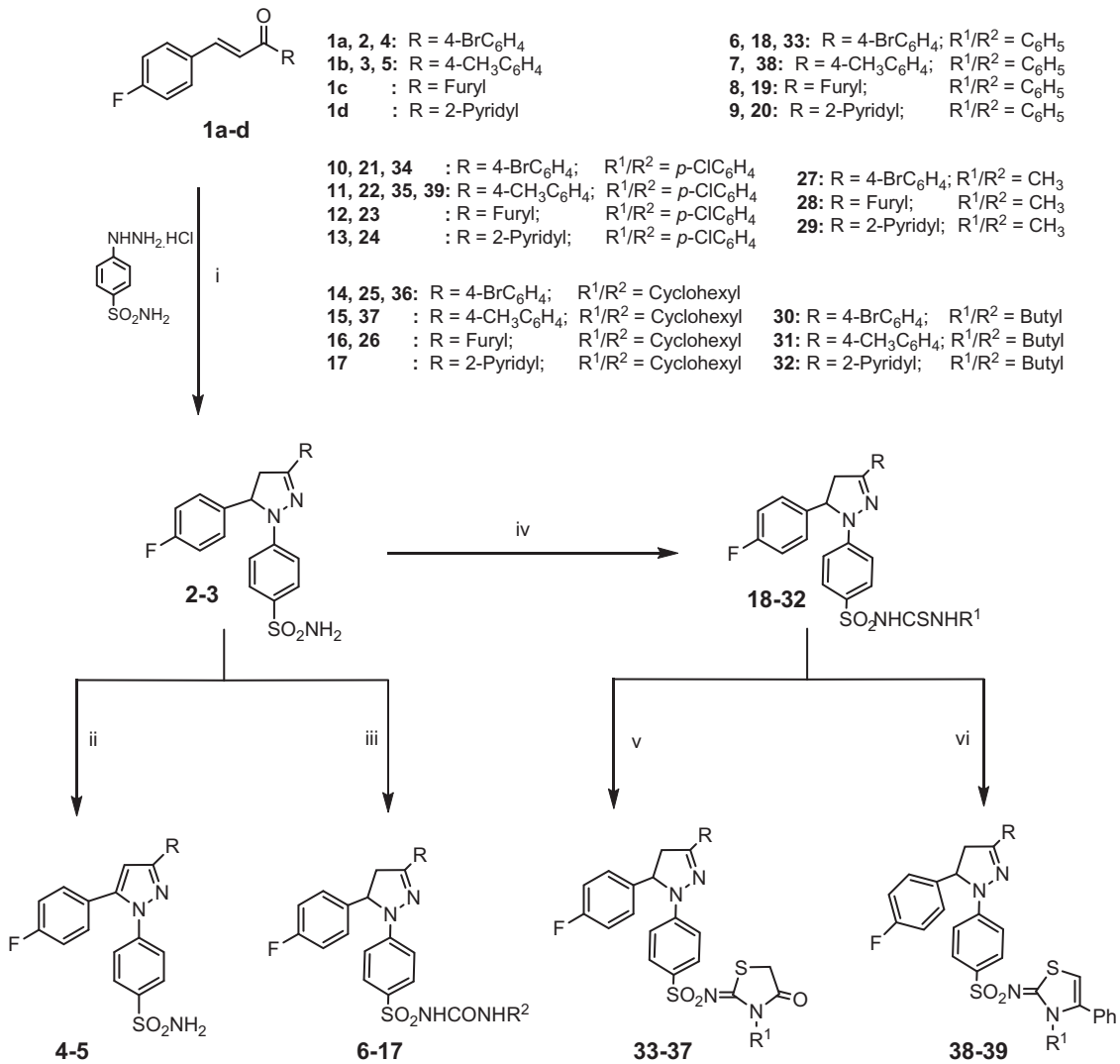
Chemistry

The condensation of the key intermediates, *p*-sulfonylphenylhyrazine hydrochloride with fluorochalcones **1a–d** afforded 5-fluorophenyl-3-aryl-1-(*p*-sulfonylphenyl)pyrazolines **2–3** (Scheme 1 and Table S1) in good yields. Oxidation of the above pyrazolines **2–3** with bromine water afforded the corresponding pyrazole derivatives **4–5**.

The IR spectra of the above pyrazoline and pyrazole derivatives displayed two absorption bands at 3237–3242 cm^{-1} and 3354–3372 cm^{-1} indicative of the NH_2 group, in addition to the strong bands at 1338–1361 cm^{-1} and 1145–1156 cm^{-1} for the SO_2N moiety. In agreement with the suggested structures, the ^1H NMR spectra of the pyrazoline derivatives **2–3** exhibited besides the aromatic protons, three multiplets (each of one proton intensity) at δ 5.32–5.38, 3.14–3.18 and 3.86–3.98. The low field multiplet is assigned to H-5 of the pyrazoline; however, the other two multiplets are due to H-4. The structures of the above compounds **2–3** were further confirmed from their ^{13}C NMR data which showed the expected number of aromatic carbons signals as well as two other signals at δ43.28–43.75 and 62.77–63.03 for (C-4) and (C-5), respectively.

The ^1H NMR spectra of the pyrazole derivatives **4–5** displayed the signals attributed to aromatic protons at δ 6.78–8.17, but lacked signals characteristic of H-4 and H-5 of the corresponding pyrazolines. The structures of compounds **4–5** were further confirmed by their ^{13}C NMR data which exhibited only aromatic carbons.

Condensation of pyrazoline derivatives **2–5** with the appropriate isocyanate and isothiocyanate in dry acetone yielded the corresponding benzene urea **6–17** and thiourea **18–32** derivatives, respectively. The IR spectra of these compounds exhibited two



Reagents and reaction conditions: i: EtOH, 3h, reflux; **ii:** Br_2/H_2O; 30 min + 3h, r.t.; **iii:** anhyd K_2CO_3, dry acetone, isocyanate, 18h, reflux; **iv:** anhydrous K_2CO_3, dry acetone, isothiocyanate, 10h, reflux; **v:** Abs. EtOH, ethyl bromoacetate, 2h, reflux; **vi:** Abs. EtOH, phenacyl bromide, anhyd NaOAc, 3h, reflux.

Scheme 1: Synthesis of compounds **2–39**.

bands at 1342–1364 cm^{-1} and 1148–1170 cm^{-1} due to SO_2N group and a urea carbonyl band at 1648–1655 cm^{-1} and a thiourea carbonyl absorption at 1137–1148 cm^{-1} for compounds **6–17** and **18–32**, respectively. The structures of the above compounds (**6–32**) were further supported by their elemental analyses (Table S1), ^{1}H NMR (Table S2) and ^{13}C NMR spectral data (Table S3).

It has been reported that condensation of *N*,*N*-disubstituted thiourea with chloroacetic acid, its chloride or bromide esters afforded 2-imino-4-oxothiazolidines, and the reaction proceeds through the intermediate formation of the cyclic pseudothiohydantoic acid[31–33]. In the present study, cyclization of the thiourea derivatives **18–32** with ethyl bromoacetate, and α-bromoacetophenone afforded the corresponding 4-oxothiazolidine **33–37** and thiazoline **38–39** derivatives, respectively. IR spectra of compounds **33–37** showed cyclic carbonyl absorption at 1718–1732 cm^{-1} and two other absorption bands at 1335–1354 cm^{-1} and 1154–1162 cm^{-1} for the SO_2N group. In addition, their ^{1}H NMR spectra showed the appearance of new methylene signal at δ 3.73–3.98 ppm for H-5 of thiazolidine ring. ^{13}C NMR spectra of these compounds showed besides the expected number of the aliphatic and aromatic carbons, a signal in the region δ 33.75–33.13 ppm corresponding to C-5 of the thiazoline moiety. The ^{1}H-NMR spectra of thiazoline derivatives **38–39** exhibited, besides the aromatic protons, a singlet of one proton intensity for H-5 of the thiazoline moiety. These structures were further supported by their ^{13}C NMR data (Table S3).

In silico calculations of molecular properties

Molecular descriptors represent the combined physicochemical, pharmacokinetic and pharmacodynamic effects of the synthesized compounds **2–39** in order to verify that these compounds exhibit good (theoretical) oral bioavailability potential. Lipinski rule of five is considered predictive for oral bioavailability; however, 16% of oral drugs violate at least one of the criteria and 6% fail in two or more[34]. The lipophilicity (milogP) and topological polar surface area (tPSA) were calculated using the online software Molinspiration[35], while the aqueous solubility, drug-likeness, drug score were calculated using the OSIRIS property explorer software[36]. Molinspiration uses sophisticated Bayesian statistics to compare structures of representative ligands active on the particular target with structures of inactive molecules and to identify substructure features (which in turn determine physicochemical properties) typical for active molecules. For the study of drug-likeness, the OSIRIS program uses a list of 5300 molecular fragments, where the frequency of occurrence of each fragment is determined based on a collection of 3300 drugs and 15 000 commercially available chemicals (Fluka) that are not drugs. tPSA was used to calculate the percentage of absorption (%ABS) according to the equation: $\%ABS = 109 - 0.345 \times TPSA$, as reported by Zhao et al.[37]. Furthermore, according to Veber et al., good bioavailability[27] is more likely for compounds with $\leq$10 rotatable bonds and TPSA of $\leq$140 Å2. Reduced molecular flexibility, as measured by the number of rotatable bonds, and low polar surface area or total hydrogen bond count (sum of donors and acceptors) are found to be important predictors of good oral bioavailability, independent of molecular weight. The calculation data are shown in Table 1.

The calculation results show that 16% of compounds meet the Lipinski rules of the five, suggesting that these compounds theoretically would not have problems with oral bioavailability. About 13% of the compounds do not follow the rule with only one violation and the rest (71%) with two violations. Compounds which had scores of less than 5 for lipophilicity, ranging from 3.51 to 4.95 for ten compounds (**2–5**, **9**, **17**, **20**, **28–29** and **32**) and 26 compounds (**6–8**, **10–16**, **18**, **19**, **21–27**, **30**, **31** and **33–37**) had scores more than 5 ranging from 5.00 to 7.54. Two compounds (**38** and **39**) have shown very high lipophilicity (>8.00). All compounds have shown a tPSA less than 140 $Å^2$, (indicating a good permeability of the drug in the cellular plasma membrane). All compounds have shown high percentage of absorption (% ABS) calculated ranged from 73.17 to 85.87% which is an indication of good bioavailability by oral route (Table 1). In Table 1, all compounds have showed Log S value less than −4.00, ranging between −4.19 and −9.72.

A positive value for drug-likeness indicates that the compound contains predominantly fragments that are often present in most currently used drugs. The drug score combines drug-likeness, lipophilicity, solubility, molecular weight and the risk of toxicity into a single numerical value that can be used to predict a global value for each compound as a potential new drug candidate. The results in the calculations show that most of the compounds gave values for drug-likeness between 2.16 and 10.13. Compounds **6–13**, **18**, **23**, **24**, **28**, **29**, **33–35** and **38** have shown very favorable drug-likeness ranging from 5.05–10.13. However, only three compounds viz., **25**, **36** and **37** have displayed negative values of drug-likeness (−1.46, −0.51 and −0.47, respectively). For comparisons, we have done similar calculations of reference drugs as well. The OSIRIS property explorer calculation indicated that almost all compounds showed a very significant druglikeness either comparable to the standard antidiabetic, drugs phenformin and 3,5-dimethylpyrazole or higher than these drugs.

All compounds showed positive values in the drug score calculation, the values ranged from 0.09 to 0.61. Even those compounds which have shown negative drug-likeness have displayed positive drug scores (Table 1). The results show that these compounds, especially compounds **2–24**, **27–35**, **38** and **39** have potential as new drug candidates. Moreover, besides violations of Lipinski's ''Rule-of-Five'' and Veber's ''criteria for good bioavailability'' these molecules confirm the suitability of these compounds to be used as a template for the design of target–directed drugs.

Biological evaluation

Antidiabetic activity

From the data presented in Table 2, it is obvious that the 3,5-disubstituted-benzenesulfonylurea derivatives **6**, **7**, **10**, **11**, **14** and **15** possess marked hypoglycemic activity. The potency of these compounds is more than that of phenformin, and they are much more active than the parent nonfluorinated compound 3,5-dimethylpyrazole. Compounds **11**, **14** and **15** are twice as active as Phenformin. However, compounds **5**, **35**, **37** and **38** are almost equipotent with the standard drug Phenformin. A careful examination of the 4,5-dihydro-1*H*-pyrazole nucleus suggests that the prerequisite features for the hypoglycemic activity in the present series are *p*-benzenesulfonamide, *p*-bromophenyl/*p*-tolyl and *p*-fluorophenyl substituents at positions-1, C-3 and C-5 respectively. The higher activity of compounds **6**, **7**, **10**, **11**, **14** and **15** may be attributed to the formation of sulfonylurea group at position-1, besides the optimum structural features in other positions (C-3 and C-5). A significant attenuation in the biological activity was reported when the sulfonylurea moiety is replaced by sulfonylthiourea as can be seen in compounds **18**, **21**, **22** and **25**. Furthermore, complete abolishment of the activity was reported when *p*-bromophenyl/*p*-tolyl groups were replaced by furyl or 2-pyridyl groups at position C-3. However, a marked resumption in the hypoglycemic activity was seen in compounds **33–39** after the cyclization of the thiourea group. Here, the

Table 1. Molecular properties calculation*.

	Lipinski's parameters											
Compound	miLogP†	MW‡	nON¶	nOHNH§	nviolations‖	TPSA#	% ABS*	nrotb†	volume‡	Solubility¶	Druglikeness§	Drug-Score‖
2	4.93	474.36	5	2	0	75.77	82.86	4	351.23	−5.60	3.84	0.42
3	4.57	409.49	5	2	0	75.77	82.86	4	349.90	−5.11	3.82	0.53
4	4.67	472.34	5	2	0	77.99	82.10	4	345.02	−5.95	2.16	0.42
5	4.31	407.47	5	2	0	77.99	82.10	4	343.69	−5.46	2.47	0.53
6	6.65	593.48	7	2	2	90.87	77.65	6	455.14	−7.22	5.90	0.16
7	6.29	528.61	7	2	2	90.87	77.65	6	453.81	−6.73	5.96	0.20
8	5.10	504.54	8	2	2	104.01	73.17	6	418.82	−6.07	7.27	0.28
9	4.67	515.57	8	2	1	103.76	73.20	6	433.10	−5.61	7.99	0.30
10	7.33	627.92	7	2	2	90.87	77.65	6	468.67	−7.95	8.06	0.14
11	6.96	563.05	7	2	2	90.87	77.65	6	467.35	−7.46	8.12	0.16
12	5.77	538.99	8	2	2	104.01	73.17	6	432.36	−6.80	9.43	0.21
13	5.35	550.01	8	2	2	103.76	73.20	6	446.63	−6.35	10.13	0.23
14	6.86	599.53	7	2	2	90.87	77.65	6	473.72	−7.28	3.03	0.16
15	6.50	534.66	7	2	2	90.87	77.65	6	472.40	−6.80	3.10	0.20
16	5.30	510.59	8	2	2	104.01	73.17	6	437.41	−6.13	4.42	0.28
17	4.88	521.62	8	2	1	103.76	73.20	6	451.68	−5.68	5.10	0.30
18	6.55	609.55	6	2	2	73.80	83.54	8	464.02	−7.22	5.90	0.16
19	5.00	520.61	7	2	1	86.94	79.00	8	427.70	−6.15	4.19	0.25
20	4.57	531.64	7	2	1	86.69	79.09	8	441.97	−5.70	4.83	0.27
21	7.23	643.99	6	2	2	73.80	83.54	8	477.55	−8.04	4.71	0.10
22	6.87	579.12	6	2	2	73.80	83.54	8	476.23	−7.55	4.74	0.12
23	5.68	555.06	7	2	2	86.94	79.00	8	441.23	−6.89	6.17	0.15
24	5.25	566.08	7	2	2	86.69	79.09	8	455.51	−6.43	6.82	0.16
25	7.40	615.59	6	2	2	73.80	83.54	8	482.60	−7.37	-1.46	0.09
26	5.84	526.66	7	2	2	86.94	79.00	8	446.28	−6.22	0.06	0.19
27	5.49	547.48	6	2	2	73.80	83.54	7	409.17	−5.80	4.36	0.32
28	3.94	458.54	7	2	0	86.94	79.00	7	372.85	−4.64	5.82	0.57
29	3.51	469.57	7	2	0	86.69	79.09	7	387.13	−4.19	6.48	0.61
30	6.93	589.56	6	2	2	73.80	83.54	10	459.57	−6.64	2.65	0.17
31	6.57	524.69	6	2	2	73.80	83.54	10	458.25	−6.14	2.71	0.21
32	4.95	511.65	7	2	1	86.69	79.09	10	437.53	−5.03	4.76	0.33
33	6.86	649.57	7	0	2	82.42	80.56	6	490.47	−7.98	5.63	0.17
34	7.54	684.01	7	0	2	82.42	80.56	6	504.00	−8.71	5.47	0.15
35	7.18	619.14	7	0	2	82.42	80.56	6	502.68	−8.22	5.52	0.18
36	7.07	655.62	7	0	2	82.42	80.56	6	509.05	−7.70	-0.51	0.12
37	6.71	590.75	7	0	2	82.42	80.56	6	507.73	−7.21	-0.47	0.14
38	8.97	644.80	6	0	2	67.04	85.87	7	552.18	−8.99	5.05	0.15
39	9.20	679.24	6	0	2	67.04	85.87	7	565.72	−9.72	5.20	0.14
Phenformin**	0.43	205.26	5	6	1	97.78	75.27	6	198.34	−0.97	3.93	0.35
3,5-Dimethylpyrazole††	0.762	96.13	2	1	0	28.68	99.10	0	97.99	−0.93	1.78	0.55

Calculated absorption (% ABS), polar surface area (PSA), LogS, Lipinski's parameters, drug-likeness and drug score of the compounds **2–39**.
*mipc – Molinspiration Property Calculator.
†Molinspiration (miLogP2.2 – November 2005).
‡Molecular weight.
¶Number of hydrogen-bond acceptors (O and N atoms).
§Number of hydrogen-bond donors (OH and NH groups).
‖Number of rule of 5 violations.
#Topological polar surface area.
*Percentage of absorption: % ABS = 109 − (0.345 × TPSA).
†Number of rotatable bonds.
‡Molecular volume.
¶Solubility prediction (LogS).
‖Fragment-based drug-likeness.
#Drug score combines drug-likeness, cLogP, logS, molecular weight and toxicity risks in one handy value.
**Positive control antidiabetic agent.
††Positive control hypoglycemic agent.

geometric factor becomes an important variable in regaining the biological profile of these derivatives. It is considered worthwhile to mention here that in general there is a remarkable increase in the hypoglycemic activity of the above 3-aryl-5-fluorophenylpyrazole derivatives **2–39** when compared with the corresponding 3,5-diarylpyrazole and 3,5-dimethylpyrazole analogs. The pronounced hypoglycemic activity of compounds **6**, **7**, **10**, **11**, **14** and **15** was further substantiated by higher values of druglikeness and drug-scores (Table 1) and make them promising candidates for future drug discovery study.

Conclusions

In this paper, several new 5-fluorophenylpyrazoles and their urea and thiourea derivatives were synthesized. Cyclization of the thiourea derivatives with the appropriate reagent afforded the corresponding cyclic compounds. Preliminary biological testing of these compounds revealed that compounds **6**, **7**, **10**, **11**, **14** and **15** showed marked hypoglycemic activities. The incorporation of fluorophenyl group is justified by a comparative study with the non-fluorinated analogs. The fluorinated analogs were found to be

Table 2. Antidiabetic activity of pyrazole derivatives.

Compd.	Reduction in plasma glucose level, %	*p*
2	7	<0.01*
3	6	<0.01*
4	8	<0.01*
5	9	<0.01*
6	16	<0.01*
7	19	<0.01*
10	18	<0.01*
11	20	<0.01*
14	21	<0.01*
15	23	<0.01*
18	<1	0.05
21	<1	0.05
22	2.5	0.05
25	3	0.05
27	4	0.05
30	2	0.05
31	1.5	0.05
33	7.5	0.01*
34	8	0.01*
35	9	0.01*
36	8	0.01*
37	10	0.01*
38	9.5	0.01*
39	7	0.01*
Phenformin	10	<0.01*
3,5-Dimethylpyrazole	4	<0.05*

*Statistically significant.

more active than their non-fluorinated counterparts. The molecular and biological properties calculations (Molinspiration and OSIRIS) revealed that all compounds showed positive values in the drug score calculation and favorable drug-like profiles. The Molecular descriptors calculation results show that compounds **2**–**24**, **27**–**35**, **38** and **39** have potential as new drug candidates.

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Declaration of interest

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