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Note

Synthesis, insecticidal and antimicrobial activities of some heterocyclic derivatives of quinazolinone

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Some new 4-phenyl-2,3-dihydro-6-(substitutedaminoethyl)-10-iodo[1,2,4]-triazino[2,3-*c*]-quina-zolin-5-ones **6-14** have been synthesized from 4-(phenyl-2,3-dihydro-6-methyl-10-iodo [1,2,4]-triazino[2,3-*c*]quinazolin-5-one **5** by introducing different heterocyclic nuclei. Compounds **5** and **6-14** have been screened for insecticidal, anti-fungal and antibacterial activities. Compound 4-phenyl-2, 3-dihydro-6-(β-naphthylaminoethyl)-10-iodo[1, 2, 4]-triazino[2,3-*c*]-quinazolin-5-one **14** has been found to be the most potent compound of the present study which shows mortality of insects at 190.6 min while standard compounds exhibit at 280 min at a concentration of 5 g/L. Moreover, this compound also possesses anti-bacterial activity. The structures of these compounds have been elucidated by IR, ^{1}H NMR, mass spectroscopy and elemental analysis.

Keywords: Triazinoquanizolinone, *Periplaneta americana*, insecticidal acitivity, antifungal, antibacterial activity

IPC Code: Int. Cl.[8] C07D

Quinconazole, sebuthylazine, fluquinconazole and nicotine derivatives of quinazolinone, triazine, triazole and pyridine, respectively, have been used as pesticidal agents[1]. It has been found in the recent literature, that quinazolinone moiety is associated with a broad spectrum of biological activity *viz* pesticidal[2], antifungal[3], insecticdal[4], antibacterial[5], anticonvulsant[6], *etc*. Furthermore, derivatives of triazine[7], naphthalene[8], pyridine[9], triazole[10], *etc.* have also been found to exhibit promising insecticidal acitivity. In view of these observations, it was decided to synthesize new 4-phenyl-2,3-dihydro-6-(substitutedaminoethyl)-10-iodo[1,2,4]-triazino[2, 3-*c*]-quinazolin-5-ones by incorporating different heterocyclic nuclei like naphthalene, pyridine, triazole, phenothiazine, *etc*. at 2-position of quinazolinone moiety and these compounds were evaluated for insecticidal, antifungal and antibacterial activity.

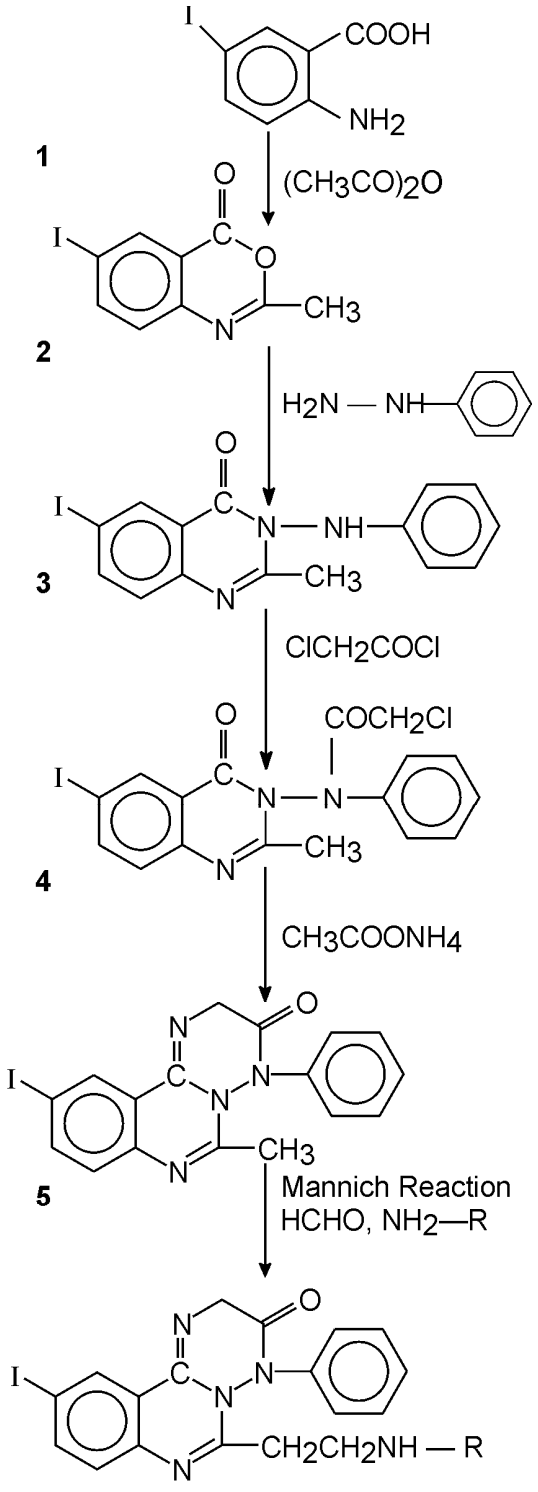
The reaction sequence leading to the formation of different quinazolinone derivatives is outlined in **Scheme I**. The reaction of 2-amino-5-iodobenzoic acid **1** with acetic anhydride yielded the desired 2-methyl-6-iodo-4*H*-3,1-benzoxazin-4-one **2**, which was converted into 3-Anilino-2-methyl-6-iodoquinazolin-4-(3*H*)-one **3** on treatment with phenyl hydrazine. Compound **3** on treatment with chloroacetyl chloride afforded 3-(*N*-chloro-acetyl)anilino-2-methyl-6-iodo-quinazolin-4(3*H*)-one **4**, which was further converted into 4-phenyl-2,3-dihydro-6-methyl-10-iodo[1,2,4]-triazino[2,3-*c*]quina-zolin-5-one **5**. Finally, this compound was cyclized to furnish 4-phenyl-2,3-dihydro-6-(substitutedamino-ethyl)-10-iodo[1, 2, 4]-triazino[2,3-*c*]-quinazolin-5-ones **6-14** *via* Mannich reaction using different substituted heterocyclic amines. The structures of these compounds were confirmed by spectral (IR, ^{1}H NMR, MS) and elemental (C, H, N) analysis.

Results and Discussion

Compounds **5** and **6-14** have been evaluated *in vivo* for insecticidal activity against male or female cockroaches (*Periplaneta americana*). These compounds were also assayed *in vitro* for their antifungal activity against *Aspergillus fumigatus*, *Candida albicans ATCC 2091*, *Candida krusei GO3*, *Candida albicans ATCC 10231*, *Candida glabrata HO5* and antibacterial activity against *Escherichia coli ESS 2231*, *Staphylococcus aureus 209p*.

Insecticidal activity

The insecticidal activity was determined by microlitre syringe method[11]. The cockroaches of either sex were divided in groups having five cockroaches each. An acetone solution (0.02 mL of 5 g/L) of standard insecticide, parathion, and different test compounds were injected on the ventral side of the insect, between the fourth and fifth abdominal segments with the help of a microlitre syringe. Insects receiving 0.02 mL of acetone by the same route served as control. The treated cockroaches were kept under observation to record the time taken until 100% mortality. During this period, no food was given. In another set of experiments, test compound **14**, 0.02 mL of 10 g/L and 20 g/L solution in acetone,


I
COOH
NH2
1
(CH3CO)2O
O
C
O
I
CH3
N
2
H2N — NH
O
C
N — NH
I
CH3
N
3
ClCH2COCl
O
COCH2Cl
C
N — N
I
CH3
N
4
CH3COONH4
N
O
C
N
N
I
CH3
N
5
Mannich Reaction
HCHO, NH2—R
N
O
C
N
N
I
CH2CH2NH — R
N
6 - 14
R = Different heterocycles

Scheme I

were also injected to other groups of insects and compared with identical doses of parathion with respect to the killing time. The statistical significance of the difference between the data of standard and test compounds was calculated by employing student's 't' test.

Antifungal activity

The *in vitro* antifungal screening of compounds against different strains of fungi like *Aspergillus fumigatus, Candida albicans ATCC 2091, Candida albicans ATCC 10231, Candida Krusei GO3* and *Candida glabrata HO5* was carried out empoying agar disc diffusion method[12]. All the compounds with standard fluconazole were treated at a concentration of 250μg/mL. 10 % DMSO in methanol was used as solvent control and sabouraud dextrose agar was used as culture medium.

Antibacterial activity

The antibacterial activity was determined *in vitro* by filter paper disc diffusion method method[13] by measuring inhibition zone in mm. All the tested compounds with standard chloramphenicol were screened for antibacterial activity against bacterial strains *Staphyloccous aureus 209p* and *Escherichia coli ESS 2231* at a concentration of 250 μg/mL. Nutrient agar was used as culture medium.

Experimental Section

All reagents and anhydrous solvents were generally used as received. Reactions were routinely performed in oven-dried glassware. Melting points were determined with an electro thermal melting point apparatus and are uncorrected. The homogeneity of all newly synthesized compounds was checked by thin layer chromatography (TLC) on silica gel-G coated plates. The eluent was a mixture of benzene and methanol in different proportions, and spots were visualized with iodine vapour. IR spectra (KBr pellet) were recorded on Bruker–IFS–66 FTIR instrument. ^{1}H NMR spectra were recorded on JEOL, GSX-400 FT NMR instrument at 400 MHz in $CDCl_3$ or DMSO-d_6 unless otherwise specified, and chemical shifts (δ) are reported in ppm relative to tetramethylsilane as an internal standard. Mass spectra were recorded on Mass Finniganmat 8230 MS mass spectrometer. Elemental analysis (C, H, N) of all the compounds was performed on Carlo Erba-1108 elemental analyzer and results were found within + 0.4% of theoretical values.

2-Amino-5-iodobenzoic acid 1. This compound was prepared according to the method of Klemme and Hunter[14]. A solution of anthranilic acid (25 g) in water (500 mL) containing potassium hydroxide (15 g) was added to a solution of iodine (46.5 g) in water (250 mL) having potassium hydroxide (24.75 g). To this solution, glacial acetic acid (100 mL) was added and the reaction mixture immediately diluted with water (120 mL), a solid separated was filtered, washed with sodium bisulphite (25 mL) and purified by recrystallization from a mixture of methanol/water. Compound **1**: m.p. 210°C (Lit. m.p. 210-11°C); yield 86.8%. Anal. Found: C, 31.75; H, 2.15; N, 5.65. Calcd for $C_7H_6NO_2I$: C, 31.93; H, 2.28; N, 5.32%. IR(KBr): 3515.440 (O-H), 3250.807 (N-H), 3015.817 (C-H aromatic), 1705.572 (C=O), 1565.093 (C⋯C of aromatic ring), 1135.617 (C-N), 513.329 cm^{-1} (C-I); ^{1}H NMR ($CDCl_3$): δ 11.05 (ss, 1H, Ar-COOH, exchangeable with D_2O), 7.30-7.11 (m, 3H, Ar-H), 6.10 (s, 2H, NH_2, exchangeable with D_2O); MS: m/z 263 $[M]^+$.

2-Methyl-6-iodo-4*H*-3,1-benzooxazin-4-one 2. Benzooxazinone has been synthesized by following the procedure of Bogert and Seil[15]. A mixture of anthranilic acid (0.01 mole) and acetic anhydride (0.02 mole) was refluxed for 4 hr and then acetic anhydride was distilled off and the viscous mass triturated with petroleum ether (40-60ºC) to afford the compound **2**: m.p. 155°C (Lit. m.p. 154-55°C); yield 75%. Anal. Found: C, 37.78; H, 2.39; N, 5.09. Calcd for $C_9H_6NO_2I$: C, 37.63; H, 2.09; N, 4.88%. IR (KBr): 3012.038 (C-H aromatic), 2925.297 (C-H aliphatic), 1710.052 (C=O), 1610.214 (C=N), 1562.136 (C⋯C of aromatic ring), 1133.150 (C-N), 536.458 cm^{-1} (C-I); ^{1}H NMR ($CDCl_3$): δ 7.32-7.10 (m, 3H, Ar-H), 1.62 (s, 3H, CH_3); MS: m/z 287 $[M]^+$.

3-Anilino-2-methyl-6-iodoquinazolin-4(3 *H*)-one 3. Compound **2** (0.01 mole) and phenylhydrazine (0.01 mole) were dissolved in absolute enthanol (70 mL). This solution was refluxed for 12 hr, concentrated, cooled and poured into crushed ice and filtered. The solid thus obtained was purified by recrystallization from ethanol to give compound **3**: m.p. 215°C; yield: 70%. Anal. Found: C, 47.95; H, 2.85; N, 10.92. Calcd for $C_{15}H_{12}N_3OI$: C, 47.75; H, 3.18; N, 11.4%. IR (KBr): 3235.733 (N-H), 3010.894 (C-H aromatic), 2923.048 (C-H aliphatic), 1709.748 (C=O), 1612.938 (C=N), 1560.189 (C⋯C of aromatic ring), 1135.349 (C-N), 530.106 cm^{-1} (C-I); ^{1}H NMR ($CDCl_3$): δ 7.65-7.26 (m, 8H, Ar-H), 5.90 (s, 1H, NH,

exchangeable with D_2O), 1.60 (s, 3H, CH_3); MS: m/z 377 $[M]^+$.

3-(*N*-Chloroacetyl) anilino-2-methyl-6-iodoquinazolin-4(3*H*)-one 4. To a solution of compound **3** (0.01 mole) in DMF (60 mL), chloroacetyl chloride (0.02 mole) was added dropwise with stirring at 0-5ºC. Then the reaction mixture was refluxed for 14 hr and excess of solvent was removed by distillation. Residue was poured into ice. The solid which separated out was purified by recrystallization from benzene/petroleum ether to obtain compound **4**: m.p. 178°C; yield 65%. Anal. Found: C, 45.10; H, 2.72; N, 9.38. Calcd for $C_{17}H_{13}N_3O_2ClI$: C, 44.98; H, 2.87; N, 9.26%. IR(KBr): 3059.450 (C-H aromatic), 2919.799 (C-H aliphatic), 1725.832 (C=O), 1594.040 (C=N), 1547.347 (C⋯C of aromatic ring), 1157.115 (C-N), 1018.180 (N-N), 693.778 (C-Cl), 528.797 cm^{-1}(C-I); ^{1}H NMR ($CDCl_3$): δ 7.70-6.85 (m, 8H, Ar-H), 4.60 (s, 2H, CH_2), 1.65 (s, 3H, CH_3); MS: m/z 453 $[M]^+$.

4-Phenyl-2, 3-dihydro-6-methyl-10-iodo[1, 2, 4]-triazino[2,3-*c*]-quinazolin-5-one 5. An equimolar mixture of compound **4** (0.01 mole) and ammonium acetate (0.01 mole), in ethanol (65 mL), in presence of few drops of gl. acetic acid, was refluxed for 8 hr. The reaction mixture was distilled off, cooled and poured into cold water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to yield compound **5**: m.p. 205°C; yield 54%. Anal. Found: C, 48.96; H, 3.36; N, 13.24. Calcd for $C_{17}H_{13}N_4OI$: C, 49.04; H, 3.13; N, 13.46%. IR (KBr): 3059.027 (C-H aromatic), 2918.745 (C-H aliphatic), 1700.938 (C=O), 1625.710 (C=N), 1594.400 (C⋯C of aromatic ring), 1154.326 (C-N) 1019.388 (N-N), 529.801 cm^{-1} (C-I); ^{1}H NMR ($CDCl_3$): δ 7.66-7.28 (m, 8H, Ar-H), 3.65 (s, 2H, CH_2 of triazine ring), 1.52 (s, 3H, CH_3); MS: m/z 416 $[M]^+$.

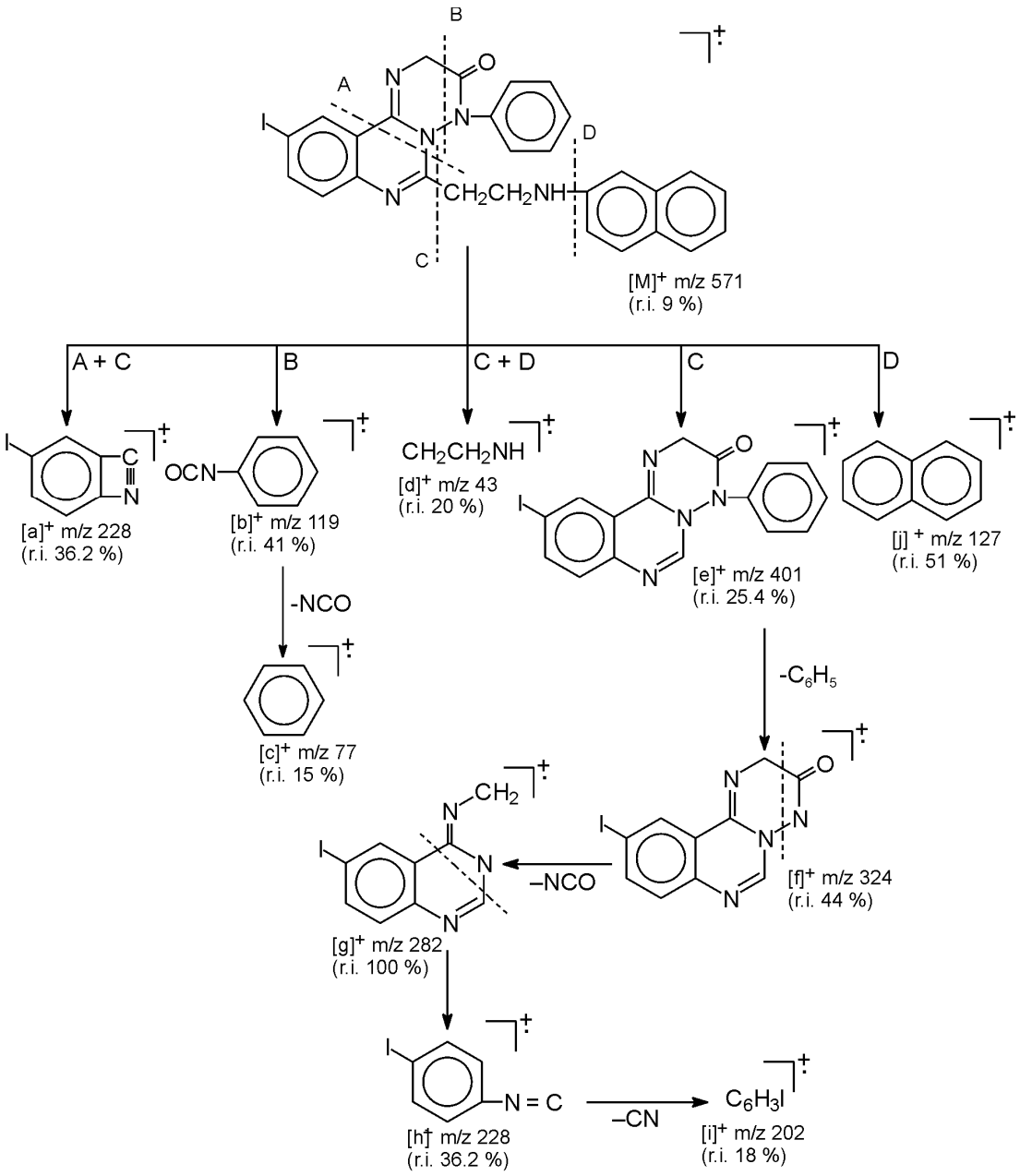
4-Phenyl-2, 3-dihydro-6-(β-naphthylaminoaminoethyl)-10-iodo[1, 2, 4]-triazino[2, 3-*c*]quinazolin-5-ones 14. A solution of compound **5** (0.01 mole) in absolute ethanol (50 mL) with β-aminonaphthalene (0.02 mole) and formaldehyde (0.02 mole) was refluxed for 8 hr, while progress and completion of the reaction was monitored by TLC. After distillation, the reaction mixture was cooled, poured over crushed ice and then filtered. The solid thus separated was purified by recrystallization from ethanol to furnish compound **14**. By this procedure, compounds **6-13** were obtained starting from α-naphthylamine, 3-aminoindole, 2-methyl-6-bromoquinazolin-4(3*H*)-one, substituted triazole, 2-aminopyridine, 10-{[5′-amino-(1′,3′,4′-oxadiazol-2′-yl)]methyl} phenothiazine, 2-amino-5-(3′-indolylmethyl)-1,3,4-thiazole, phenothia-zine and β-aminonaphthalene, respectively. Their physical and analytical data are given in **Table I**. Compound **14**: m.p. 82ºC; yield 52%. Anal. Found: C, 58.66, H, 3.61; N, 12.48. Calcd for $C_{28}H_{22}N_5OI$: C, 58.84, H, 3.85; N, 12.26%. IR (KBr): 3310.243 (N-H), 3015.029 (C-H aromatic), 2926.848 (C-H aliphatic), 1710.981 (C=O), 1603.430 (C=N), 1575.342 (C⋯C of aromatic ring), 1028.708 (N-N) 536.807 cm^{-1}(C-I); ^{1}H NMR (DMSO-d_6): δ 7.75-6.80 (m, 15H, Ar-H), 5.45 (brs, 1H, NH, exchangeable with D_2O), 5.0-4.90 (m, 4H, CH_2CH_2), 3.62 (s, 2H, CH_2 of triazine ring).

Under electron impact the molecule **14** undergoes fragmentation of any or several of its bonds simultaneously. **Scheme II** shows the fragmentation routes that explain the major peaks of the mass spectrum.

The general feature of the mass spectrum is that compound **14** gives the molecular ion peak $[M]^+$ at m/z 571, which is further decomposed *via* different routes to give different fragments as follows. According to cleavage A+C across the quinazolinone moiety, fragment $[a]^+$ has been observed with m/z 228. Route-B consists of splitting through triazine ring to yield isocyanate radical $[b]^+$ at m/z 119, which readily ejects neutral isocyanate species to give rise to phenyl radical $[c]^+$at m/z 77.

Cleavage C+D gave fragment $[d]^+$ with m/z 43. Further, C-pattern of cleavage was observed, which gave ion $[e]^+$ at m/z 401. A phenyl radical is eliminated from ion $[e]^+$ to produce fragment $[f]^+$ with m/z 324. The neutral isocyanate molecule is seen to be eliminated from ion $[f]^+$ to give fragment $[g]^+$ at m/z 282 as a base peak. Ion $[g]^+$ exhibited splitting *via* quinazolinone nucleus to yield ion $[h]^+$ with m/z 228, which was similar to ion $[a]^+$. And finally neutral cyanide radical has been ejected from $[h]^+$ fragment to give ion $[i]^+$ with m/z 202.

Naphthalene radical $[j]^+$ at m/z 127 has also been observed after disintegration of molecular ion *via* route-D. The above fragmentation pattern of quinazolinone and triazine nuclei, somehow, has similarities to the fragmentation routes of the same molecules reported by Prasad and Khan[16] and Guidoni *et al.*[17], respectively.



Scheme II

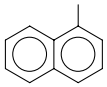
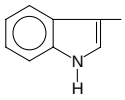
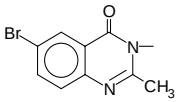
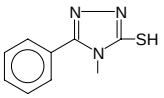
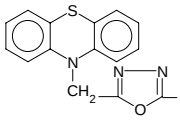
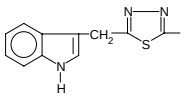
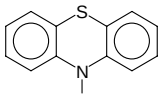
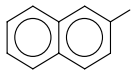
Insecticidal activity against *Periplaneta americana*

Ten substitued quinazolinone derivatives **5-14** and standard parathion were screened at a concentration of 5 g/L (**Table I**). All the compounds except **13** exhibited statistically sigfnificant insectiddal activity. Compound **14** was found to be the most potent insecticidal agent, that is why this compound along with parathion was further evaluated at two different concentrations *i.e.* 10 g/L and 20 g/L. Interestingly, compound **14** possessed better insecticidal activity than the standard at all the tested concentrations.

Antifungal activity

The newly synthesized compounds **5-14** were also assayed *in vitro* for antifungal activity. Only compounds **6**, **8**, **10** and **13** were found to be active against *A. fumigatus, C. albicans* ATCC 10231, *C. albicans* ATCC 2091, *C. Krusei* G03 and *C. glabrata*

Table 1 — Characterization data and insecticidal activity of compounds **5-14**

Compd.	R	m.p. °C	Yield (%)	Recryst. Solvent	Molecular Formula	Found (Calcd.) % C	H	N	Insecticidal activity Concen-tration	Mean killing time (min)
5.		205	54	ethanol	$C_{17}H_{13}N_4OI$	48.96 (49.04	3.36 3.13	13.24 13.46)	5 g/L	485 ± 15.14***
6		96	60	Methanol	$C_{28}H_{22}N_5OI$	59.10 (58.84	3.89 3.85	11.92 12.26)	5 g/L	212.8 ± 6.80**
7		140	55	Ethanol	$C_{26}H_{21}N_6OI$	55.82 (55.71	3.58 3.75	15.10 15.00)	5 g/L	266 ± 3.72*
8		113	45	Acetone	$C_{27}H_{21}N_7O_2BrI$	47.78 (47.51	2.92 3.08	14.66 14.37)	5 g/L	374 ± 7.39***
9		124	48	Ethanol	$C_{26}H_{21}N_8OSI$	50.60 (50.32	3.10 3.39	17.91 18.06)	5 g/L	440.6 ±10.31***
10		218	50	Ethanol	$C_{23}H_{19}N_6OI$	53.10 (52.87	3.90 3.64	15.8 16.09)	5 g/L	225.4 ± 5.20**
11		105	52	Methanol	$C_{33}H_{25}N_8O_2SI$	54.48 (54.70	3.59 3.45	15.28 15.47)	5 g/L	309.8 ± 6.29*
12		130	45	Methanol	$C_{29}H_{23}N_8OSI$	52.61 (52.89	3.36 3.50	17.38 17.02)	5 g/L	344 ± 8.16**
13		111	55	Methanol	$C_{30}H_{23}N_6OSI$	56.33 (56.07	3.42 3.58	13.20 13.08)	5 g/L	256.4 ± 6.46
14		82	52	Ethanol	$C_{28}H_{22}N_5OI$	58.66 (58.84	3.61 3.85	12.48 12.26)	5 g/L 10 g/L 20 g/L	1906 ± 5.72*** 175 ± 7.07*** 162 ± 6.81***
[@] Control									0.02 mL	720 ± 10.29
Parathion									5 g/L 10 g/L 20 g/L	280± 11.74 $^{\Delta\Delta\Delta}$ 247± 9.29 $^{\Delta\Delta\Delta}$ 231± 13.75 $^{\Delta\Delta\Delta}$

n = 5 in each group; P < 0.05, P < 0.01, P < 0.001 in comparison to control; ; * P < 0.05, ** P< 0.01, *** P < 0.001 in comparison to standard; [@] acetone.

Table II — Antifungal and antibacterial activities of compounds **5-14** by filter paper disc and agar diffusion methods, respectively

Compd	Antifungal activity[#] [Diameter of the inhibition zone (mm)]					Antibacterial activity[#] [Diameter of the inhibition zone (mm)]	
	Aspergillus fumigatus	*Candida albicans* ATCC 2091	*Candida albicans* ATCC 10231	*Candida krusei* G03	*Candida glabrata* H05	*Staphyloc-occus aureus* 209p	*Eschericia coli* ESS 2231
[@]Control	0	0	0	0	0	0	0
Fluconazole	0	29	25	19	15	—	—
Chloramp-phenicol	—	—	—	—	—	20	20
5	0	0	0	0	0	0	0
6	10	15	20	0	09	0	0
7	0	0	0	0	0	10	09
8	08	11	15	0	10	0	0
9	0	0	0	0	0	0	0
10	11	09	15	0	10	0	0
11	0	0	0	0	0	0	0
12	0	0	0	0	0	08	10
13	14	12	10	0	14	0	0
14	0	0	0	0	0	15	09

[#]Concentration was 250 μg/mL.
[@]10% DMSO in methanol.
—: No activity done.
0: No inhibition zone.

H05. None of compounds possessed better activity than Fluconazole (**Table II**).

Antibacterial Activity

Antibacterial activity of the compounds **5-14** was performed on *S. aureus* 209 p and *E. Coli* ESS 2231 at a concentration of 250 μg/mL. Only three compounds **7**, **12** and **14** exhibited antibacterial activity, but none of them showed a larger inhibition zone than the standard used (**Table II**).

Conclusion

Structure-activity relationship of the compounds **5-14** revealed that conversion of compound 4-phenyl-2,3-dihydro-6-methyl-10-iodo [1,2,4]-triazino [2,3-*c*]-quinazolin-5-one **5** into different substituted compounds 4-phenyl-2,3-dihydro-6-(substituted-aminoethyl)-10-iodo[1,2,4]-triazino [2,3-*c*]-quinazolin-5-ones **6–14** *via* Mannich reaction markedly enhanced the insecticidal activity (**Table I**). It is evident from the results obtained that compounds **6**, **7**, **10**, **13** and **14** substituted with α-aminonaphthalene, 3-aminoindole, 2-aminopyridine, phenothiazine and β-aminonaphthalene, respectively, at 6-position of 1,2,4-triazinoquinazolinone moiety showed better insecticidal profile than parathion (**Table I**), and additionally compounds **6**, **10** and **13** possessed good antifungal activity, while compounds **7**, **12** and **14** exhibited antibacterial activity. However, antifungal and antibacterial activity associated with the above mentioned compounds are not more than standard used for each. By analysing the results, it can be concluded that among these compounds none simultaneously possessed antifungal and antibacterial activity (**Table II**), although these compounds displayed prominent insecticidal activity.

Furthermore, it has been observed that the difference in the structure of the compounds **6** and **14** is of α-aminonaphthalene and β-aminonaphthalene moieties, respectvely. It is significant to mention that compound **14** exhibited potent insecticidal activity in comparison to parathion at all concentrations tested, along with antibacterial profile. Hence, it can be concluded that substitution pattern of naphthalene at β-position enhances the insecticidal activity than at α-substituted naphthalene.

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