Part 1: SYNTHESIS AND REACTIONS OF SOME NEW PYRAZOLO[4,5-D]IMIDAZOLE DERIVATIVES AND SCREENING THEIR ANTIBACTERIAL AND ANTITUMOR ACTIVITIES

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Abstract

Reaction of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one with diazotized aromatic amines gave the corresponding diazenyl derivatives 1, which were condensed with carbonyl compounds to give the arylidene derivatives 2. Reaction of the parent pyrazolone with urea, thiourea and guanidine gave the pyrazoloimidazole derivatives 3. compound 3a reacted with thiourea in DMF to give the thiourea derivative 4. The reaction of 4 with malonic acid and acetyl chloride gave the pyrimidinedione derivative 5, which on reaction with thiourea in presence of sodium ethoxide gave the triazine derivative 6. S-alkylation of 6 with ethyl chloroacetate gave the ethyl acetate derivative 7, which on hydrolysis gave the corresponding acid, derivative8 and on reaction with hydrazine hydrate gave the corresponding acetohydrazide 9. the reaction of compound 9 with salicylaldehyde gave the pynazolidinone 10, while with carbon disulphide in alkaline solution it gave the oxadiazole thione 11 respectively. Some of the new compounds showed antimicrobial and antitumor activities.

Keywords: Pyrazoloimidazole, pyrimidinedione, triazine, antimicrobial, antitumor.

Introduction

A large number of pyrazoles are reported to exhibit CNS depressant[(1)], antibacterial[(2)], antitumor[(3)] and antagonists[(4)] activities, while imidazoles exhibit antimicrobial[(5)], antitumor[(6)], antiproliferative[(7)] activities, and also act as inhibitors of copper corrosion[(8)] and as optoelectronic materials[(9)]. This prompted the authors to use 1-phenyl-3-methyl-1H-pyrazol-5(4H)-one as the key intermediate in the synthesis of new fused pyrazoloimidazole derivatives to screen their antimicrobial and antitumor activities.

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded with a Pye Unicam SP3-200 spectrophotometer. ^{1}H-NMR were measured with a Varian EM60

and Jeol-9 MHz instrument using TMS as internal standard and the mass spectra were measured with a FINNI-Gas 3300 mass spectrometer. The synthesis of various compounds are outlined in Schemes 1 and 2.

Synthesis of 3-methyl-1-phenyl-1H-pyrazole-4,5-dione 4-[N-(4-substituted phenyl)hydrazone] (1a-c).

A cold solution of the appropriate diazotized aromatic amine (0.01 mol), namely p-tolyldiazenyl, p-anisyl diazenyl, p-diazenyl benzoic acid and/or was added gradually to a cold solution of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (0.01) dissolved in pyridine (50 ml). The reaction mixture was kept in the ice chest for 2 h, with constant stirring. The solid obtained was filtered, washed with water and recrystallized from ethanol (1a m.p. 130˚C, 1b m.p. 132°C, 1c m.p. 128˚C). Analysis for $C_{17}H_{16}N_{14}O$ (%); Calcd: C, 69.86, H 5.48, N 19.18; found: C, 69.84, H 5.46, N 19.16; for $C_{17}H_{16}N_4O_2$ (%); Calcd: C, 66.23, H, 5.19, N, 18.19; found C, 66.20, H, 5.17, N, 18.17; for $C_{17}H_{14}N_4O_3$ (%); Calcd: C, 63.35, H, 4.35, N, 17.39; found: C 63.33, H, 4.33, N, 17.37.

Synthesis of the arylidene derivatives (2a-g).

To a solution of 1a and/or 1b (0.01 mol) in sodium ethoxide solution [from sodium (0.02 mol in absolute ethanol (20 ml)], aldehyde and/or ketone (0.01 mol) namely benzaldehyde, salicylaldehyde, furfural o-vaniline, acetylacetone and/or benzoyl acetone was added while stirring. The reaction mixture was then refluxed for 2 h. The solid that separated often cooling was filtered and recrystallized from ethanol (2a m.p. 165˚C, 2b m.p. 172˚C, 2c m.p. 170˚C, 2e m.p. 170˚C, 2f m.p. 120˚C or propanol (2d m.p. 190˚C, 2g m.p. 240˚C). Analysis for $C_{24}H_{20}N_4O$ (%): Calcd. C 75.79, H 5.26, N 14.74; found C 75.77, H 5.24, N 14.72; for $C_{24}H_{20}N_4O_2$ (%): Calcd. C 72.73, H 5.05, N 14.14; found C 72.71, H 5.03, N 14.12; for $C_{24}H_{20}N_4O3$ (%): Calcd C 69.90, H 4.85, N 13.59 ; found C 69.78, H 4.83, N 13.57; for $C_{22}H_{18}N_4O_2$ (%): Calcd. C 71.35, H 4.86, N 15.14; found C 71.33, H 4.84, N 15.12; for $C_{25}H_{22}N_4O_3$ (%): Calcd. C 70.42, H 5.16, N 13.15; found C 70.40, H 5.14, N 13.13; for $C_{22}H_{22}N_4O_2$ (%): Calcd. C 70.59, H 5.88, N 14.97; found C 70.57, H 5.86, N 14.95; for $C_{27}H_{24}N_4O_2$ (%): Calcd. C 74.31, H 5.50, N 12.84; found C 74.30, H 5.49, N 12.82.

Synthesis of 3-methyl-1-phenyl-4,6-dihydroimidazo[4,5-c]pyrazol-5-yl derivatives (3a-d).

A mixture of 3-methyl -1-phenyl-1H-pyrazol-5(4H)-one and/or 3-methyl-1H-pyrazol-5(4H)-one (0.01 mol), 10% sodium hydroxide (10 ml), absolute ethanol (20 ml), thiourea, urea and/or guanidine (0.01 mol) was refluxed for 6 h. The solid that separated was filtered off and recrystallized from ethanol (3a m.p. 130˚C, 3b m.p. 122˚C, 3c m.p. 133˚C, 3d m.p. 140˚C). Analysis for $C_{11}H_{10}N_4S$ (%): Calcd. C 57.39, H 4.35, N 24.35, S 13.91; found: C 57.37, H 4.33, N 24.33, S 13.90; for $C_5H_6N_4S$ (%): Calcd. C 38.96, H 3.90, N 36.36, S 20.78; found C 38.94, H 3.92, N 36.38, S 20.80, for $C_{11}H_{10}N_4O$ (%): Calcd. C 61.68, H 4.67, N 26.17; found C 61.66, H 4.65, N 26.15; for $C_{11}H_{11}N_5$ (%): Calcd C 61.97, H 5.16, N 34.86; found C 61.99, H 5.14, N 34.84.

Synthesis of N-(3-methyl-1-phenyl-1,6-dihydroimidazo[4,5-c]pyrazol-5-yl) thiourea (4)

A mixture of 3a (0.01 mol) and thiourea (0.01 mol) in DMF (30 ml), was refluxed for 16 h., cooled then poured onto ice. The solid obtained was filtered off and recrystallized from ethanol to give (4) (m.p. 190˚C). Analysis for $C_{12}H_{12}N_6S$ (%): Calcd. C 52.90, H 4.40, N 30.90, S 11.80; found C 52.50, H 4.20, N 30.60, S 11.50.

Synthesis of 1-acetyl-3-(3-methyl-1-phenyl-1,6-dihydroimidazo[4,5-c] pyrazol-5-yl)-2-thioxodihydro-4,6-(1H,5H) pyrimidinedione (5)

A mixture of 4 (0.01 mol), malonic acid (0.01 mol) and acetyl chloride (1 ml) was heated on a water-bath for 2 h, cooled then poured onto ice. The solid obtained was filtered off and recrystallized from ethanol to give (5) (m.p. 210˚C). Analysis for $C_{17}H_{14}N_6O_3S$ (%): Calcd. C, 53.40, H 3.70, N 22.00, S 8.40; found C 53.20, H 3.50, N 22.2, S 8.30.

Synthesis of 4-methyl-7-(3-methyl-1-phenyl-1,6-dihydroimidazo[4,5-c] pyrazol-5-yl)-2,6-dithioxo-1,2,6,7-tetrahydro-8H-pyrimido[1,6-a]-1,3,5-triazin-8-one (6)

A mixture of 5 (0.01 mol), thiourea (0.01 mol) and sodium ethoxide solution [from sodium (0.01 mol) in absolute ethanol (30 ml)] was refluxed for 8 h., cooled

then poured onto ice. The solid obtained was filtered off and recrystallized from ethanol to give (6) (m.p. 188°C). Analysis for $C_{18}H_{14}N_8OS_2$ (%): Calcd. C, 51.18, H 3.31, N 26.54, S 15.17; found C 51.20, H 3.30, N 26.52, S 15.15.

Synthesis of ethyl-2- [(3-methyl-1-phenyl -1, 6-dihyroimidazo [4,5-c] pyrazol-5-yl) sulfanyl] acetate (7)

A mixture of 3a (0.01 mol) and ethyl chloroacetate (0.015 mol) in dry acetone (50 ml) containing anhydrous potassium carbonate (0.03 mol) was heated on a water bath for 24 h. The reaction mixture was filtered while hot then the excess solvent was evaporated under reduced pressure. The solid obtained was recrystallized from ethanol to give (7) (m.p. 205˚C). Analysis for $C_{15}H_{16}N_4O_2S$ (%): Calcd. C, 57.0, H 5.1, N 17.7, S 10.1; found C 57.2, H 5.00, N 17.5, S 10.0.

Synthesis of 2-[(3-methyl-1-phenyl-1,6-dihydroimidazo[4,5-c] pyrazol-5-yl) sulfanyl] acetic acid (8)

A mixture of 7 (0.01 mol) and sodium hydroxide (0.032 mol dissolved in 4 ml of water) in ethanol (50 ml) was refluxed for 3 h. After cooling the reaction mixture was acidified with dilute HCl. The solid that separated was filtered, washed with water and recrystallized from ethanol to give (8) (m.p. 196˚C). Analysis for $C_{13}H_{12}N_4O_2S$ (%): Calcd. C 54.17, H 4.17, N 19.44, S 11.11; found C 54.15, H 4.14, N, 19.40, S 11.10.

Synthesis of 2- [(3-methyl-1-phenyl-1,6- dihydroimidazo [4,5-c]pyrazol-5-yl)sulfanyl] acetohydrazide (9)

To a solution of 7 (0.01 mol) in absolute ethanol (25 ml), hydrazine hydrate (0.01 mol) was added and the reaction mixture was refluxed for 6 h. The solid that separated after concentration and cooling was recrystallized from propanol to give (9) (m.p. 215˚C). Analysis for $C_{13}H_{14}N_6OS$ (%): Calcd. C 51.70, H 4.60, N 27.80, S 10.60; found C 51.68, H 4.40, N 27.50, S 10.40.

Synthesis of 5-(2-hydroxyphenyl)-4-[(3-methyl-1-phenyl-1,3a-dihydroimidazo [4,5-c] pyrazol-5-yl)sulfanyl]-3-pyrazolidinone (10)

A mixture of (9) (0.01 mol), salicylaldehyde (0.01 mol) and absolute ethanol (25 ml) was refluxed for 6 h. After cooling and removing the excess solvent under reduced pressure, the solid obtained was recrystallized from ethanol to give (10) (m.p 220°C).

Analysis for $C_{20}H_{18}N_6O_2S$ (%): Calcd. C 59.10, H 4.40, N 20.70, S 18.82; found C 59.00, H 4.20, N 20.50, S 18.80.

Synthesis of 5- [(3-methyl-1-phenyl-1,6-dihydroimidazo[4,5-c] pyrazol-5-yl) sulfanyl] methyl -1,3,4-oxadiazole-2(3H)-thione (11)

To a suspension of (9) (0.01 mol) in ethanol (15 ml) was added carbon disulfide (5 ml) and powered KOH (0.005 mol) and the reaction mixture was refluxed on a water bath for 6 h., cooled then poured onto ice and acidified with few drops of dilute HCl. The solid obtained was recrystallized from ethanol to give (11) (m.p. 198˚C). Analysis for $C_{14}H_{12}N_6OS_2$ (%): Calcd. C 48.8, H 3.5, N 24.4, S 18.6; found C 48.6, H 3.3, N 24.2, S 18.4.

Antimicrobial activity

Antimicrobial activity of compounds 1a, 3a, 4, 5, 9, 10 and 11 was tested by the disk diffusion method. Whatman No.1 filter paper disks were sterilized by autoclaving for one hour at 140˚C. Sterile disks were impregnated with tested compounds. Agar plates were uniformly surface inoculated by fresh broth cultures of Staphylococcus aureus and Escherichia coli (as Gram positive strains), Bacillus sbutilis (as Gram negative strains), Candida albicans (as yeast), Aspergillus funigatus (as fungi). Impregnated disks were placed on the medium, suitably spaced apart, and the plates were incubated at 5˚C for 1h to permit good diffusion and then transferred to an incubator at 28˚C for 24 h. The zones of inhibition were measured. DMF was used as a solvent and chloramphenicol was used as a standard antibacterial agent and terbinafin was used as standard antifungal agent[10].

Antitumor activity

The method used is that trypan blue exclusion[11]

Procedure

1 ml of tumor cells which is drawn from mice bearing (E.A.C)

1) In sterile test tubes, where 2.5 x 10^5 tumor cells/ml were suspended in phosphate buffer saline.
2) 3 Different concentrations for each compound (25, 50, 100 mg/ml).
3) Added 2.5 x 10^5 tumor cells for each tube.
4) Incubate at 37°C for 2 hours.
5) From sample cells + trypan blue volume by volume on slide.
6) Examine under microscope.

7) Dead cells stained blue and live cells not stained.
8) Then carried out to calculate the percentage of non viable cells.

Results and Discussion

The reaction of 1-phenyl-3-methyl-1H-pyrazolo-5(4H)-one with aromatic diazonium chloride derivatives gave the corresponding diazenyl compounds (1a-c), through elimination of HCl and rearrangement. The structure of the diazenyl derivatives was derived from the IR spectrum of 1a which showed bands for C=O at 1650, C=N at 1600 and NH at 3372 cm^{1}. The ^{1}H-NMR (DMSO-d_6) spectrum of 1a exhibited signals at δ (ppm): 8.87-7.18 (9H, m, Ar-H), 2.49 (3H, s, CH_3 of pyrazolone) and 2.12 (3H, s, Ar-CH_3). The mass spectrum of (1a) showed the parent ion peak at m/z 292 (73.5%).

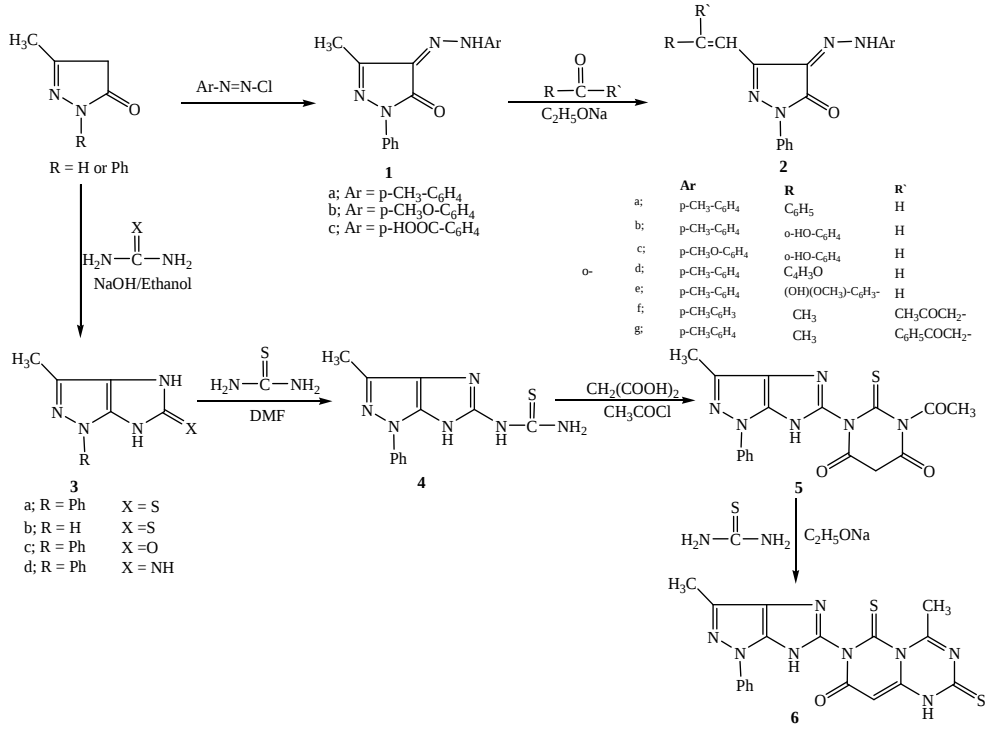
The condensation of the diazenyl derivatives (1a and 1b) with carbonyl compounds namely benzaldehyde, salicylaldehyde, furfural, o-vanilin, acetyl acetone and/or benzoyl acetone in presence of sodium ethoxide gave the arylidene derivatives 2a-g. Their IR spectra showed bands at 1656-1644, 1605-1581, 3281-3264 cm^{-1} for C=O, C=N and NH. The ^{1}H-NMR (DMSO-d_6) spectrum of 2b exhibited signals at δ (ppm): 6.53-6.48 (13H, m, Ar-H), 2.28 (3H, s, CH_3), 2.48 and 2.5 (2H, 2 x d, -CH=CH-), 10.25 (s, 2H, NH and OH). The mass spectrum of 2b showed the parent ion peak at m/z 396 (12.1%).

As stated above pyrazole and imidazole derivatives displayed a wide spectrum of pharmacological activities. In the present work, the reaction of 1-phenyl-3-methyl-1H-pyrazol-5(4H)-one and/or 1H-pyrazolo-3-methyl-5(4H)-one with thiourea, urea and/or guanidine in alkaline medium gave the corresponding pyrazolo imidazole derivatives 3a-d. The IR spectrum of 3a showed bands at 1615, 1258 for C=N and C=S. The ^{1}H-NMR (DMSO-d_6) spectrum of 3a exhibited signals at δ (ppm): 7.83-7.03 (5H, m, Ar-H), 2.13 (3H, s, CH_3), while its mass spectrum showed the parent ion peak at m/z 230 (61.9%).

Compound (3) exists in a thione-thiol tautomerism. The existence of the thiol form was proved by its reaction with thiourea in boiling DMF to give the thiourea derivative (4), through the nucleophilic attack by nitrogen of thiourea to the carbon of the thione moiety followed by elimination of one mole of H_2S. Its IR spectrum showed bands at 1598, 1223, 3421 cm^{-1}(broad) for C=N, C=S and NH_2 + NH, its ^{1}H-NMR (DMSO-d_6) spectrum exhibited signals at δ (ppm): 7.77-7.20 (5H, m, Ar-H), 2.15 (3H, s, CH_3), while its mass spectrum showed the parent ion peak at m/z 272 (65.22%).

The structure of (4) was further confirmed by its reaction with malonic acid and acetyl chloride to give the pyrimidinedione derivative (5), which is in accordance with a previous publication[12]. Its IR spectrum showed bands at 1715, 1704, 1598,, 1234, 3397 cm^{-1} for $COCH_3$, CO, C=N, C=S and NH. Its ^{1}H-NMR (DMSO-d_6) spectrum exhibited signals at δ (ppm): 7.78-7.23 (5H, m, ArH), 2.28 (3H, s, CH_3), 2.48 (3H, s, $COCH_3$), 3.61 (2H, s, CH_2), while its mass spectrum showed the parent ion peak at m/z 382 (75%).

Compound (5) was used as a starting material for the preparation of the triazine derivative (6). Thus the reaction of 5 with thiourea in presence of sodium ethoxide gave the triazine derivative (6). The IR spectrum showed bands at 1730, 1625, 1250, 3451 cm^{-1} for C=O, C=N, C=S, NH.



Scheme 1

The thiol form of 3 was also confirmed by its reaction with ethyl chloroacetate in boiling dry acetone containing anhydrous potassium carbonate to give the S-alkylated product 7. Its infrared spectrum was devoid of $^{\nu}$C=S and showed the characteristic C=O (ester) at 1739. cm^{-1} the ^{1}H-NMR (DMSO-d_6) spectrum exhibited signals at δ (ppm): 7.84-7.37 (5H, m, Ar-H), 3.94 (2H, s, SCH_2CO), 2.44 (2H, q,

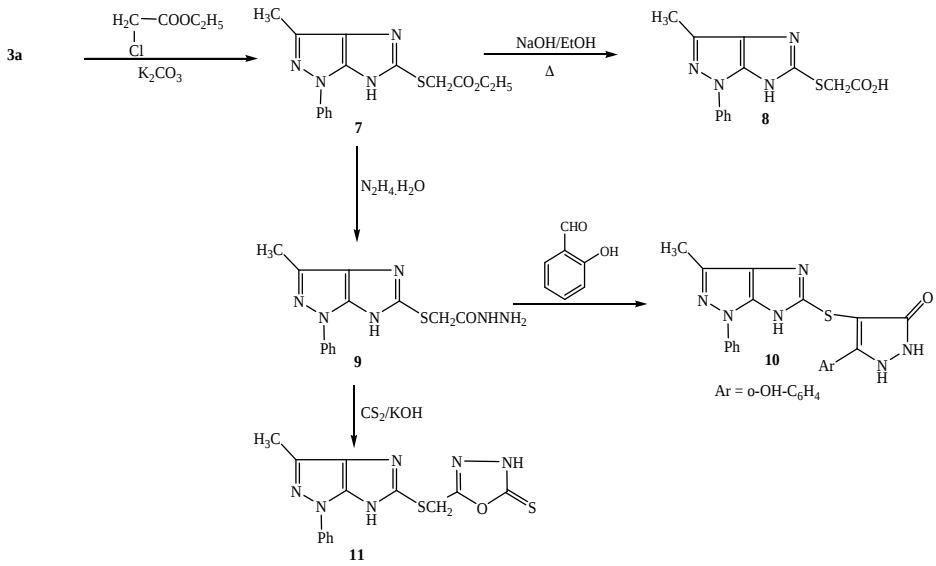
$CH_3\underline{CH_2}$), 1.82 (3H, t, $\underline{CH_3}CH_2$), 2.13 (3H, s, CH_3), 11.9 (1H, s, NH), while its mass spectrum showed M – $CH_3]^+$ at m/z 301 (59%).

The structure of 7 was chemically confirmed by alkaline hydrolysis to give the corresponding acid (8). Its IR spectrum was devoid of C=O (ester) and showed bands at 1706, 1597, 3415 cm^{-1} (broad) for C=O (acid), C=N, NH + OH.

Further confirmation for compound 7 was its reaction with hydrazine hydrate to give the hydrazide derivative (9). Its IR spectrum showed bands at 1701, 1598, 3064 cm^{-1} (broad) for C=O (amide), C=N, NH_2 + NH, while its mass spectrum showed M – $2]^+$ at m/z 300 (22.05%).

Compound 9 was used as key intermediate for the introduction of new heterocyclic rings. Thus, the reaction of 9 with salicylaldehyde gave the pyrazolidinone derivative (10). The IR spectrum showed bands at 1741, 1597, 3394 cm^{-1} (broad) for C=O, C=N, NH + OH.

Furthermore, compound (9) underwent ring closure reaction with carbon disulfide to give the oxadiazole thione derivative (11). Its IR spectrum showed bands at 1597, 1180, 3395 cm^{-1}(broad) for C=N, C=S, NH.



Scheme 2

The results of antimicrobial activity tests are listed in Table 1.

From the table the pyrazolone derivatives were slightly effectives among the tested. while compounds 3a, 9, 10 and 11 against Bacillus sbutilis gave moderate results.

The results of screening antitumor activity tests are listed in Table 2. From the table compounds 3a, 7, and 11 showed good antitumor activity.

Table (1) Antimicrobial activity of some compounds

Sample	**1a**			**3a**			**4**			**5**			**9**			**10**			**11**		
.Conc	**1**	**5**	**2.5**	**1**	**5**	**2.5**	**1**	**5**	**2.5**	**1**	**5**	**2.5**	**1**	**5**	**2.5**	**1**	**5**	**2.5**	**1**	**5**	**2.5**
	mg/ml			**mg/ml**			**mg/ml**			**mg/ml**			**mg/ml**			**mg/ml**			**mg/ml**		
Staphylococcus aureus	0	0	0	++	+	0	+	0	0	0	0	0	++	+	0	+	+	+	++	+	+
Escherichia coli	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bacillus sbutilis	+	+	0	++	++	++	+	0	0	0	0	0	++	+	+	++	+	+	++	++	+
Candida albicans	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Aspergillus funigatus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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Table 2: Antitumor activity of the compounds using (E.A.C)

Sample	**Inhibition of cell viability %**		
	µg/ml		
	100	**50**	**25**
3a	96%	80%	60%
5	0	0	0
7	97%	80%	69%
9	70%	30%	10%
11	97%	79%	63%

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الملخص العربى

الجزء الأول: تشييد وتفاعلات بعض مشتقات البيرازلو [4,5 – د] إميدازول الجديدة ومسح النشاط البكتيرى والسرطانى لها.

تفاعل 3 – ميثيل -1- فنيل – 1 H ـ بيرازول ـ 5 ـ (4H) ـ أون مع الأمينات الأرومانية تعطى مشتقات الديازونيل 1.

بينما تفاعلها مع مركبات الكربونيل تعطى مشتقات الأريلدين 2.

تفاعل خماسى البيرازولون مع اليوريا، الثيويوريا، والجوانيدين يعطى مشتقات البيرازولو إميدازول 3.

مركب 3أ يتفاعل مع الثيويوريا فى وجود DMF ليعطى مشتق الثيويوريا 4.

تفاعل مركب 4 مع حمض المالونيك والأستيل كلوريد يعطى مشتق
البيريميدين ديون 5.

الذى يكون تفاعله مع الثيويوريا فى وجود إيثوأكسيد الصوديوم يعطى مشتق
الترايزين 6.

S-ألكيلايشن للمركب 6 مع إيثيل كلورواسيتات يعطى مشتق الإيثيل أسيتات 7.

الذى يعطى بالهيدروليسيس مشتق الحمض المقابل 8.

والذى يعطى بتفاعله مع الهيدرازين هيدرات الأسيتوهيدرازيد 9.

تفاعل المركب 9 مع سالسيلأ لدهيد يعطي بيراز وليدينون 0.10 بينما مع الكربون داي سلفات في محلول قلوي يعطي أكسادايا زول ثيون 11 . بعد المركبات الجديدة لها نشاط بكتيري ونشاط سرطاني .