



New Series of Substituted Heterocyclics Derived from α, β – Unsaturated Ketone and Their Cytotoxic Activity Tumor Cell Lines

Volume 34, Number 6

Muna S. AL-Rawi , Huda A. Hassan, Dheefaf F. Hassan and Ismaeel Y. Majeed

Department of Chemistry, College of Education For Pure Science Ibn Al- Haitham, University of Baghdad, Baghdad-Iraq.

Corresponding Author E-mail: tagreedaloom@gmail.com

DOI : <http://dx.doi.org/10.13005/ojc/340620>

Article Publishing History

Article Received on : 30-09-2018

Article Accepted on : 06-11-2018

Article Published : 10 Nov 2018

Article Metrics



ABSTRACT:

The aldol condensation of 2-acetylnaphthalene with 9-anthracene carboxaldehyde afforded α, β -unsaturated keton (1) . New heterocyclic compounds containing: cyclohexenone[2], indazole[3], pyrimidinethion [4], thiazolo fused pyrimidine[5], isoxazoline[6], substituted pyrazoline[7]_{a-d} and pyrimidinone[8] rings system were synthesized from α, β -unsaturated keton[1]. Cyclization of [1] with ethylacetacetate gave the mentioned heterocycle cyclohexanone [2]. The cyclo condensation of [2] with hydrazine gave the new indazole derivative [3]. furthermore, the reaction of [1]with thiourea gives thiopyrimidine derivative [4]. The cyclo condensation of [4] with chloroacetic acid gave the fused rings [5]. Then reacted compound[1] with hydroxylamine to produce isoxazoline [6]. Also the reaction of [1]with hydrazine and hydrazide derivatives to produce pyrazole [7]_{a-d}. All the newly synthesized derivatives[2-7_{a-d}] were characterized via the CHN-S, FT- IR, ¹H NMR, and ¹³C NMR (of some of theme). The antibacterial and cytotoxic activities were evaluated for these derivatives[2-7_{a-d}] . The study of antibacterial displayed good to moderate activity and the study of anticancer activity showed that were effective for inhibition of L₂₀ B the mice intestines carcinoma cell line and RD human pelvic rhabdomyosarcoma cell line. Treated.

KEYWORDS:

α, β -Unsaturated ketons; Anti-Cancer Activity; Cyclohexenone; Indazole; Isoxazoline; Pyrazoline; Pyrimidinone;Pyrimidinethion

Download this article as:



Copy the following to cite this article:

AL-Rawi M. S, Hassan H. A, Hassan D. F, Majeed I. Y. New Series of Substituted Heterocyclics Derived from α,β – Unsaturated Ketone and Their Cytotoxic Activity Tumor Cell Lines. Orient J Chem 2018;34(6).

Copy the following to cite this URL:

AL-Rawi M. S, Hassan H. A, Hassan D. F, Majeed I. Y. New Series of Substituted Heterocyclics Derived from α,β – Unsaturated Ketone and Their Cytotoxic Activity Tumor Cell Lines. Orient J Chem 2018;34(6). Available from: <http://www.orientjchem.org/?p=52371>

Introduction

α,β – Unsaturated ketons, one of the primary classes of natural products and belongs to flavonoid family, as well these compounds keep several biological activities.^{1,2} α,β -Unsaturated ketons are suitable for the synthesis of an important heterocyclics rings like cyclohexenone, indazole, pyrimidinethion, isoxazoline, pyrazoline, and pyrimidinone.³ The biological activity for chalcones are wide ranging in the recent years, isoxazolines are considered biologically active molecules since they are used in controlling parasite infections in humans⁴ in addition to their use as insecticides,⁵ nematocides and molluscicides agents.⁶ Pyrazolines, for example, have attracted increasing attention due to their pharmaceutical applications such as: anti-bacterial, anti-fungal, enzymatic inhibitors and cytotoxic properties.⁷⁻⁹ Pyrimidine derivatives play an essential role in medicinal field due to their anti-inflammatory, anti-ulcerogenic.¹⁰ The anti-inflammatory and anti-cancer activities of indazoles were also reported (11). Hence, it appeared of interest to prepare the mentioned heterocyclics linked to 2-acetyl naphthalene moiety and evaluated their cytotoxicity effect on two cancer cell lines including: L₂₀ B and RD cell lines.

Experimental

Materials

All chemicals utilized brand Sigma-Aldrich and used as received.

Instrumentation

FTIR spectra were registered in KBR discs on a SHIMADZU-FTIR-8400spectro photometer. ¹H& ¹³CNMR spectra were done on Bruker 400-MHz spector photometer. CHN-S were completed an EuroEA Elemental Analyzer.

General Synthetic Procedures



A New Edition of Web of Science
Journal Impact Factor
2022: 0.5
Five Year: 0.8

Journal is Indexed in
CABELLS
SCHOLARLY ANALYTICS
Cabells Whitelist



National Academy of
Agricultural Sciences, India
2022 NAAS Score: 5.25



CNKI Scholar
(China National Knowledge Infrastructure)

Journal Archived in:



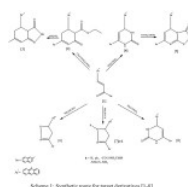
News & Events

Life Fellowship Awards in
Chemistry by Researchers Society
of Chemical Sciences, Bhopal,
India.



Membership Form of Researchers
Society of Chemical Sciences
Email: iqbalospc@yahoo.com
Click here for RSCS Details

All compounds [2-8] were synthesized confer to the scheme 1.



Scheme 1: Synthetic route for target derivatives [1-8].

[Click here to View scheme](#)

Preparation of chalcone: 3-(anthracen-9-yl)-1-(naphthalen-2-yl) prop-2-en-1-one [1]

2-Acetyl naphthalene (1.70g, 0.01 mol) was added with small portions to a solution of (2.06g, 0.01 mol) 9-anthracenecarboxaldehyde in 10% ethanolic NaOH (10 mL) and stirred for 3h. The reaction mixture was acidification with dilute HCl. The resulting product was filtered off, washed well with cold water, dried in air to give the required product [1]; Yield 82%; mp 155-157°C; FT-IR : 3049 (C-H arom.), 2931 (C-H aliph.), 1658 (C=O), 1622- 1597 (C=C) and 1172 due to (C-O-C); ¹H- NMR (δ): 8.42-7.70 (m, 16H, Ar-H), 6.20, 6.15 (2H,d, CH=CH). Furthermore, the results of CHN-S analysis harmonized with the proposed structure for [1] C₂₇H₁₈O: C, 90.47; H, 5.06; Found: C, 90.91; H, 5.63.

Synthesis of ethyl 6-(anthracen-9-yl)-4-(naphthalen-2-yl)-2-oxocyclohexa-3-ene-carboxylate [2]

A stirred mixture of chalcone [1] (3.58g, 0.01 mol), CH₃COOC₂H₅ (0.01mol), aqueous KOH solution (1mL, 10%) was heated for 3h and then left to stirring overnight at ambient temperature. The precipitated off white was collected and dried to give the cyclohexanone derivatives [2]; yield : 68% ; m.p. 182-184°C; FTIR 3035 (C-H arom.), 2981 (C-H aliph.), 1737 (C=O) 1660 (C=O) and 1604 (C=C); ¹HNMR : 8.55-6.92 (m, 16H, H-Ar), 6.69(s,1H, CH=C-Ar),4.02(1H,m,CH-Ar'), 2.71 (1H, s, CH-CO), 1.58 (s, 2H, CH₂-C-Ar), 1.24 (q,2H, -CH₂CH₃) and 1.10 (t,3H, -CH₂CH₃); Anal.Calcd. for C₃₃H₂₆O₃: C (84.23); H(5.57); Found:C(84.85); H (5.76).

Synthesis of 4-(anthracen-9-yl)-6-(naphthalen-2-yl)-2,3,4,5-tetrahydro-3H-indazol-3-one [3]

Hydrazine hydrate was added dropwise to a solution of compound[2] (4.70 g,0.01 mol) in ethanol (20 mL) and glacial acetic acid (0.3 mL) at ambient temperature. The mixture was heated for 6h(12). The pale yellow solid formed was filtered off and dried , yield:52%; m.p. 137-139°C; FT-IR(3385-NH), (3020C-H arom.), (2980 C-H aliph.), (1653 C=O) (1631 C=N) and (1955 C=C); ¹HNMR (9.78:s,1H,NH),(7.86-7.22 : m, 16H, H-Ar), (4.02:s, 1H, CH=C-Ar), (3.47 :1H, d, CH-CO), 3.18(d,2H, CH₂CH-Ar'), 1.35 (m, 1H, CH₂-CH- Ar'); likewise, the results of CHN-S analysis agree with the suggested structure for compound(3) :C₃₁H₂₂N₂O: (C:84.91); (H:5.06); (N:6.39);Found:(C:85.15); (H:5.66,(N:6.91).

Synthesis of 4-(anthracen-9-yl)-6-(naphthalen-2-yl)-3,4-dihydropyrimidine 2(1H)-thione [4]

To a solution of chalcone (3.58g) in ethanolic NaOH (0.01 mol), SC(NH₂)₂ (0.6 g) was added, refluxed for 7 hr. A solution of ice cold water was added, the orange solid created, washed with water and dried, yield :68%; m.p. 214-216 °C ; FT-IR: 3383cm⁻¹ for(NH), 3012cm⁻¹ (C-H arom.), 1638 (C=N), and 1255 (C=S). ¹HNMR: 12.00 (s,1H, NH tautomeric with SH in thiopyrimidine ring), 11.38(s,1H,NH),9.00- 7.86(m, 16H ArH), 8.29 (d ,1H, CH=C-Ar), 7.65 (d ,1H, =CH-CH-Ar); Also, the output of CHN-S analysis correspond with the indicate structure for C₂₈H₂₀N₂S.

Synthesis of 5-(Anthracen-9-yl)-7-(naphthalen-2-yl)-5H-Thiazolo [3,2-a] pyrimidin-3(2H)-one [5]

Chloroacetic acid (0.01mol) was added to a compound [4] (4.16g,0.01mol) in mixture of glacial CH₃CO₂H (10 ml) and (CH₃CO)₂O (5ml) and anhydrous sodium acetate (0.45 g). The mixture refluxed for 6h and poured into 30 mL crushed ice to allow golden yellow solid precipitate, which was filtered and dried; Yield (48%); m.p. 193-195°C; FT-IR(v .cm⁻¹): 3091 (C-Haromatic), 2098 (C-H aliphatic), 1668 (C=O), 1606 (C=N), 1078(C-S); ¹H NMR (9.55- 7.16 :m, 16H Ar-H), 8.46 (d, 1H, CH=CAr), 5.45 (d,1H, =CH-CH-Ar), 1.66(s,2H,CH₂). CHN-S for compound C₃₀H₂₀N₂OS: (C, 78.92); (H, 4.42); (N, 6.14); (S, 7.02);Found: (C,79.20); (H,4.18); (N,6.45); (S,7.42).

Synthesis of derivatives 5-(anthracen-9-yl)-3-(naphthalen-2-yl)-4,5-dihydro-isoxazole[6]

To a mixture of chalcone[1] (3.58g, 0.01mol) and hydroxyl amine hydrochloride (0.69g, 0.01mol) ethanolic sodium hydroxide (10mL) was refluxed for 8h. On cooling 50 mL water was added then the mixture acerbated at fridge overnight and the white solid was formed, yield (77%) ; m.p. 146-148°C; FT-IR3064 (C-H arom.), 1627 (C=N), 1598 (C=C); 1348 (cyclic ether) (C-O); ¹HNMR: (8.89 -7.36: m, 16H, ArH), (4.73-4.61 :d, 2H, CH₂CHAr'), (2.25-1.20 :t,1H, CH₂-CH- Ar'). The CHN analysis for C₂₇H₁₉NO: (C, 86.84); (H, 5.13); (N, 3.75); Found: (C,86.22); (H,5.45); (N,3.95).

Synthesis of 5-(naphthalen-2-yl)-3-(substituted phenyl)-pyrazoline derivatives [7] a-d

A mixture of chalcon [1] (3.58g, 0.01mol) and hydrazine hydrate or substituted hydrazine (0.01 mol) in EtOH (20 mL) containing glacial acetic acid (0.3 mL) was heated for 4h. The precipitated was formed, collected and dried to afford [7]_{a-d}.

5-(anthracen-9-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1H-pyrazole[7]_a

Yellowish brown; yield (58%) ; m.p. 92-94°C; FTIR for this compound confirm that:3431(NH), 3053 (CH -Ar), 1666 (C=N), 1593 (C=C); ¹HNMR : (9.01:s,1H, NH), (8.48-6.76: m, 16H Ar-H), 4.11 (t,1H, CH₂CHAr'), 2.49-1.46 (d,2H, CH₂-CH- Ar'), CHN analysis (C₂₇H₂₀N₂) agree with the proposed structure: C,87.07; H,5.41; N,7.52 Founder: C,87.55; H,5.85; N,7.85.

5-(anthracen-9-yl)-3-(naphthalen-2-yl)-1-phenyl-4,5-dihydro-1H-pyrazole[7]_b

dark orange; yield (60%); m.p. 149-151°C; FTIR(CH-Ar 3057), (C=N1620); ¹HNMR , 8.12 -7.23 (m, 16H ArH), 3.67 (t,1H, CH₂CHAr'), 1.19-1.35 (d,2H, CH₂-CH- Ar'); the CHN-S compound[7]_b C₃₃H₂₄N: C,88.36; H,5.39; N,6.25, Founder: C,88.99; H,5.70; N,6.05.

(2-aminophenyl)(5-(anthracen-9-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) methanone [7]_c

Brownish red; yield (74%) ; m.p. 172-174°C; FTIR: 3344(NH₂), 3026 (CH -Ar), 1666 (C=N), 1593 (C=C), 1336 (C=S); ¹HNMR : 9.32(s,1H,NH), 8.70 -7.55 (m, 16H, Ar-H), 4.27 (t,1H, CH₂CHAr'), 1.711.21 (d,2H, CH₂-CH- Ar'); CHN-S for compound C₃₄H₂₅N₃O [7]_c: C, 83.07; H, 5.13; N, 8.55; Found: C, 83.65; H, 5.42; N,8.76.

1-(5-(anthracen-9-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) thiourea [7]_d

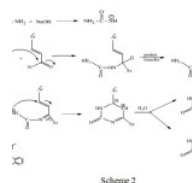
bright yellow; yield (67%) ; m.p. 204-206°C; FT-IR(v .cm⁻¹): 3309(NH₂), 3035 (C-H aromatic),1718(C=O), 1660 (C=N), 1597 (C=C); ¹HNMR : 11.47(s,1H,NH₂), 9.70 -7.45 (m, 16H Ar-H), 7.60-7.61 (t,1H, CH₂CHAr'), 1.62 (d,2H, CH₂-CH- Ar');Anal. Calcd. for C₂₈H₂₂N₄S: C, 75.31; H, 4.97; N, 12.55; S, 7.18 Founder: C, 75.73; H, 5.11; N,12.32;S,7.29.

Synthesis of 4-(anthracen-9-yl)-6-(naphthalen-2-yl)-3,4-dihydropyrimidin-2(1H)-one [8]

To a solution of chalcone [1] (3.58g, 0.01 mol), urea (0.6g, 0.01 mol) and EtOH (30 mL) containing glacial $\text{CH}_3\text{CO}_2\text{H}$ (0.3ml) was added. The combination was heated for 7h and poured into crushed ice. The solid light yellow precipitate was washed, filtered and dried to give pyrimidinone derivative[8]. Yield (75%); m.p. 119-121 $^\circ\text{C}$; FTIR: (3406,3350NH), (3064 CH arom.), (1670 C=O), (1614,1597 C=C); ^1H NMR: 10.12 (s,1H, NH), 8.82(s,1H, NH), 8.38-7.35 (m,16H, Ar-H and pyrimidine proton), 3.33 (d,1H, =CH-CH); ^{13}C NMR the presence of peaks at δ 190.88 (C=O), δ 125.11-138.96 (C aromatic) and δ 123 (CH=CH); CHNS for $\text{C}_{28}\text{H}_{20}\text{N}_2\text{O}$ the target compound: C, 83.98; H, 5.03; N, 7.00; Founder: C,83.67; H,5.43; N,7.11.

Results and Discussion

Aldehyde condensation reaction of 2-acetyl naphthalene with 9-anthracenecarboxaldehyde in alcoholic sodium hydroxide afforded 3-(anthracen-9-yl)-1-(naphthalen-2-yl) prop-2-en-1-one [1] at room temperature. The structure of the chalcone [1] was substantiated spectroscopically and elemental analyses. The formation of cyclohexanone derivative [2] was achieved by refluxing chalcone [1] with ethylacetoacetate in the presence of aqueous potassium hydroxide solution. Moreover, reaction of this derivative [2] with hydrazine hydrate in the presence of $\text{CH}_3\text{CO}_2\text{H}$ as a catalyst give a new indazol derivative [3], the reaction may have proceeded through condensation between carbonyl group of cyclohexanone [2] and amine NH_2 of hydrazine, followed by cyclization by losing a molecule of ethanol. The pyrimidinethione derivative [4] was obtained from refluxing chalcone [1] with thiourea in basic medium, its structure was ascertained by spectral data. However, compound [5] was prepared directly from the reaction [4] with $\text{ClCH}_2\text{CO}_2\text{H}$ in glacial $\text{CH}_3\text{CO}_2\text{H}$ and $(\text{CH}_3\text{CO})_2\text{O}$ in the presence of anhydrous $\text{CH}_3\text{CO}_2\text{Na}$. Isoxazoline compound [6] was synthesized from the reaction of chalcone [1] with $\text{NH}_2\text{OH}\cdot\text{HCl}$. Structure of compound [6] was established by their spectral data, the FTIR spectra were no characteristic bands of the $\text{CH}=\text{CH}$ and $\text{C}=\text{O}$ and NH groups in the starting material, with the appearance of new absorption band for (C=N) group around 1627 cm^{-1} and C-O (cyclic ether) group around 1348 cm^{-1} . It was reported that, reaction of α,β -Unsaturated ketone with N_2H_4 or PhNHNH_2 or 2-amino benzohydrazide or thiosemicarbazide in the presence of glacial acetic acid and refluxed, yield the target pyrazoline [7]a-d, respectively. The structure of the pyrazoline derivatives [7]a-d were identified by their melting point, CHN-S analysis, FTIR and ^1H NMR spectroscopy. The FTIR spectra of these compounds exhibited new absorption stretching peaks of NH and imine groups in the region 3431 cm^{-1} and $1666\text{-}1660\text{ cm}^{-1}$, the more characteristic for pyrazole ring. The pyrimidinone derivative [8] was synthesized from reaction of chalcone [1] with urea in glacial acetic acid as a catalyst. The structure of the pyrimidinone [8] characteristic by FTIR, H 1 and ^{13}C NMR spectroscopy; the suggested mechanism of this reaction may be shown as follows Scheme 2.



Scheme 2

[Click here to View scheme](#)

Antibacterial Evaluation

The target compounds were synthesized [2-8] were screened their antibacterial activity (in vitro) against both G+ and G- bacteria; like Staph. aureus (G+), Bacillus cereus (G+) and E.coli (G-) according to the agar plate diffusion method. The test solution was prepared by using DMSO as a solvent, and each compounds was dissolved in DMSO to give concentration (1ppm). The plates were then incubated at 37 $^\circ\text{C}$ and examined after 24 hrs. (+) and (++) depending upon the diameter and clarity as in Table 1. The derivatives [3],[5],[7]b,[7]d, and [8] displayed good to moderate antibacterial activity against three pathogenic species; also, the derivatives [2],[6],[7]a and [7]c shows low activity against Gram positive. Finally, both compounds [2] and [7]c shows no activity against Gram negative but they exhibited moderate to weak antibacterial against Gram positive.

Table 1: antibacterial activity of the synthesized compounds[2-8].

Comp. No.	Staphylococcus aureus(G+)	Bacillus cereus (G+)	E. Coli (G-)	Comp. No.	Staphylococcus aureus(G+)	Bacillus cereus (G+)	E. Coli (G-)
[2]	7.1	12	0	[7]a	5.5	15	6.9
[3]	20.4	16.8	6.5	[7]b	27	7.7	9.8
[4]	11.7	6.6	13.7	[7]c	10	7.5	0
[5]	18.7	13	11.9	[7]d	19.2	11	8.8
[6]	8.1	9.5	8	[8]	13.7	11.8	6.7

Key to symbols: highly active = ≤ 15 mm, moderately active = 11-15 mm and slightly active = 5-10mm.

Cytotoxic Activity

All derivatives of chalcone were chosen for examined their anticancer activity. Two cell lines were used for testing: L20B (mice intestines carcinoma) cell line and RD (human pelvic rhabdomyosarcoma) according to the procedure of Freshney.¹³ Seven derivatives [2-8] different concentrations were tested for their cytotoxicity by using cultured cells in microtiter plate (96wells). The examine was applied by the next steps:

a-Seeding

When cells in the incubated falcon became monolayer, a aliquot 200 μl /104-105 cells/well from single cell hang were added to all the 96 wells of the microtiter plates; which wrapped by plate lids and sealed with parafilm, shaken softly and returned to the incubator.

b- Incubation

Plates were incubated in moisten chamber at 37 $^\circ\text{C}$, 5% CO_2 .

c- Exposure

When the cells are in full activity, they were exposed to 6 concentrations of the derivatives $\mu\text{g/ml}$ for cell line, 200 μl of maintenance medium were added to each well of control group, then plates were locked with parafilm and returned to the incubator. cytotoxicity was carried out after 48 hr and the photo picture were taken after 24 hr.

d- Staining

Cell viability was measured after 48 hr, then removing the medium and 20 μ l/well solution of MTT were added. The crystals remaining in the wells were solubilized by the addition of 200 μ l/well of DMSO followed by incubation in 37°C for 15 min with shaking. The absorbance was measured on a microplate reader at 620 nm. The average of inhibition of cell growth was counted according to (46) as follow equation:-

$$\text{Inhibition rate} = \frac{\text{mean of control} - \text{mean of treatment}}{\text{mean of control}} \times 100$$

The synthesized derivatives [5],[7]a,[7]b,[7]c and [8] showed moderate anticancer activity against two type of cancer cell lines. The remaining derivatives exhibited low anticancer activity. However, the compound [6] showed no activity versus both cell lines, and [2] showed no activity versus RD cell line. Structure-activity relationship could be observed by examining the effect of heterocyclic rings on these derivatives on the cell growth inhibition.

Table 2: The inhibition of cells growth of synthesized derivatives. μ l/well.

Comp. No.	for (L20 B)	for (RD)	Comp. No.	for (L20 B)	for (RD)
[2]	20.0%	–	[7]a	47.8%	42.1%
[3]	15.9%	23.3%	[7]b	60.7%	33.5%
[4]	11.5%	25.7%	[7]c	18%	11.9%
[5]	52.7%	12.2%	[7]d	51.9%	32.3%
[6]	–	–	[8]	23%	34.2%

Conclusions

The aim of the present work has been directed towards synthesized of new series of heterocyclic compounds derived from α, β -un saturated ketone they may have more activity and less toxicity as anticancer agents. Biological evaluation may support the development of synthetic organic compounds and pharmaceutical chemistry. The study of antibacterial displayed good to moderate activity. All compounds except [6] showed moderate to low inhibition for L20B and RD cancer cell lines.

Acknowledgment

We thank Dr. Hytham Ahmed -Faculty of Pharmacy -Menoufia University/ Egypt for support us throughout our experimental work.

References

1. N. Beyhan, B.Kocyigit-Kaymakcioglu, S. Gu, and F. Aricioglu, Arabian Journal of Chemistry, (2017) 10, S2073–S2081. [CrossRef](#)
2. N.Prakash, M.Elamaran and N. Ingarsal, Chemical Science Transactions, (2015), 4(4), ISSN: 2278-3458,947-954.
3. . Muna S. AL-Rawi, Huda A. Hassan, Dheefaf F. Hassan and Rana M. Abdullah, International Journal for Sciences and Technology,(2013),Vol. 8, No.2, 48.
4. Sanjay Menon, Susan M. K. Shaheen and Valerie A.Lain Court, "Spiro -cyclic Isoxazolines As Anti-parasitic Agents", WO Patent, 039484 A1, (2012).
5. P hillip G.Lahm , Wagerle T. and Ming X., "Isoxazoline Insecticides " , US Patent, 0127165 A1, (2014).
6. David J. Calderwood, Eric C. Breinlinger and Steven L. Swann, Subhendu Makherjee, " Isoxazolines As Therapeutic Agents", WO Patent, 151158A1, (2012).
7. Oren M. Becker , Shritr A., Schutz N., Zeev B., Yacovan A. and Ozeri R., " Pyrazolines for the Modulation of PKM2", US patent , 0302609A1,(2013)
8. Patrich Page, Francesca Gaggini and Benoit laleu, "Pyrazoline Dione Derivatives As NADPH Oxidase Inhibitors " , US Patent, 0172352 A1, 2012
9. Mohamed EL. K., Malika B., Bouabdallah I., Abdelmajid Z.,Fouad M., Rachid T., Abdelkrim R. and AHMED M.; Natural Product Research, Vol. 21, No. 11, 2007, 947. [CrossRef](#)
10. Casey C. Maccomas , Scott D. Kuduk and Thomas S. Reger,"Pyrimidine PDE10 Inhibitors", WO Patent , 081619A1, (2014).
11. Zacharia Cheruvallath, Philip Erckson and Jun feng, " Indazole derivatives " , WO Patent, 130855A1,(2013).
12. Nehad A. Abdel Latif, Manal M. Saeed , Nesreen S. Ahmed,Rasha Z. Batran and Nadia R. A. El-Mouhty; International Journal of Innovative Research in Science,Engineering and Technology; (2014),Vol. 3, Issue 1,8517.
13. Freshney RI., "Culture of Animal Cells: A manual of Basic Technique and Specialized Applications," 6th Edition, Wiley: New York, 2010.



This work is licensed under a [Creative Commons Attribution 4.0 International License](#).

Links

Article Processing Charges
Current Issue
Editorial Board
Home
Indexed in
Policies
Aims & Scope
Article Submission Workflow
Join Our Team of Reviewers
Online Submission

Contact Us

Your Name (required)

Your Email (required)

Phone Number

Comment

Which is bigger, 5 or 8?

Google Page Rank

Page Rank 5

License



This work is licensed under a Creative Commons Attribution 4.0 International License.

XRL F

Type the above text in box below

Send